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New Enantioselective Metal-Catalysed Conjugate Addition-Initiated Reactions of Alkenyl(aza)arenes



Thesis Submitted in Accordance with the Requirement of The University
of Edinburgh for the Degree of Doctor of Philosophy

By

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in January 2010, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Signed

Aakarsh Saxena

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List of Abbreviations

Å	ångström
μw	microwave
Ac	acetyl
acac	acetylacetonate
ACP	acyl carrier protein
APCI	atmospheric-pressure chemical ionisation
app	apparent
aq.	aqueous
Ar	aryl
barf	$[\text{B}\{3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3\}_4]^-$
BBN	borabicyclo(3.3.1)nonane
Bn	benzyl
Boc	<i>t</i> -butyloxycarbonyl
br	broad
<i>c</i>	concentration
C	celsius
<i>ca.</i>	<i>circa</i>
calcd	calculated
cat.	catalyst
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
CuH	copper hydride
d	doublet
dan	1,8-naphthalenediaminato

DEMS	diethoxymethylsilane
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dpm	dipivaloylmethane
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv.	equivalent
ES	electrospray
ESI	electrospray ionisation
EWG	electron-withdrawing group
FT	Fourier transform
g	gram
h	hours
HBTU	<i>O</i> -(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
IR	infrared spectroscopy

L_n	ligand
LDA	lithium diisopropylamide
<i>m</i>	<i>meta</i>
m	multiplet
M	molar concentration
mg	milligram
min	minute
mL	millilitre
m.p.	melting point
MHz	megahertz
MIDA	<i>N</i> -methyliminodiacetic acid
NHC	<i>N</i> -heterocyclic carbene
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
<i>o</i>	<i>ortho</i>
OAc	acetate
<i>p</i>	<i>para</i>
pin	pinacol
PMHS	polymethylhydrosiloxane
PMP	4-methoxyphenyl
ppm	parts per million
psi	pound-force per square inch
q	quartet
<i>rac</i>	<i>racemic</i>

RCAA	rhodium-catalysed asymmetric hydroarylation
rt	room temperature
s	singlet
S _N Ar	nucleophilic aromatic substitution
t	triplet
TBS	<i>t</i> -butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMDS	tetramethyldisiloxane
TMS	trimethylsilyl
t _r	retention time
Ts	tosyl
UV	ultraviolet spectroscopy

Abstract

I. Enantioselective Rhodium-Catalysed Arylation of Electron-Deficient Alkenylarenes

β -substituted alkenyl-*para*-nitroarenes, an unexplored substrate class for catalytic asymmetric addition reactions, undergo highly enantioselective rhodium-catalysed arylations with arylboronic acids in the presence of a dibenzylamide-containing chiral diene ligand. One example of the asymmetric arylation of an alkenyl-*p*-cyano-*m*-(trifluoromethyl)benzene is also reported. The scope of this process is broad with variation in the β -position of the alkene, additional substituents on the electron-deficient arene, and sterically and electronically unique arylboronic acids all tolerated. The synthetic utility of the developed methodology is demonstrated by smoothly converting one arylated product into its corresponding indole via the Bartoli reaction.

II. Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes with Ketones

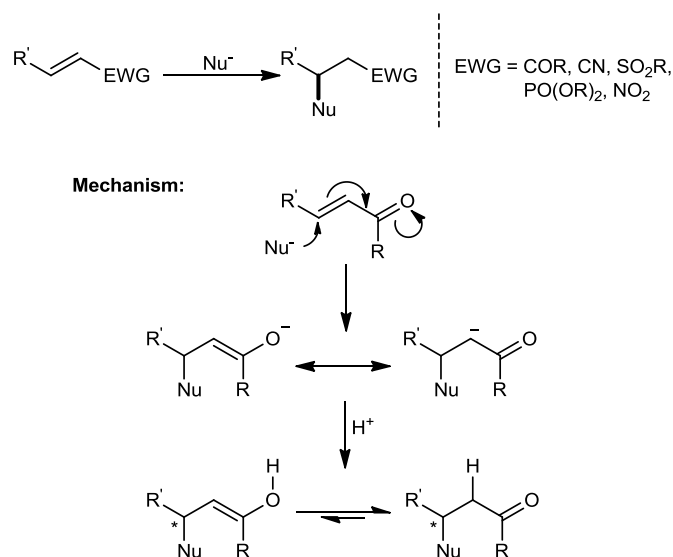
Catalytic enantioselective methods for the preparation of chiral azarene-containing compounds are of high value. By combining the utility of copper hydride catalysis with the ability of C=N-containing azaarenes to activate adjacent alkenes toward nucleophilic additions, the enantioselective reductive coupling of alkenylazaarenes with ketones has been developed. The process is tolerant of a wide variety of azaarenes and ketones, and provides aromatic heterocycles bearing tertiary-alcohol-containing sidechains with high levels of diastereo- and enantioselection.

I. Enantioselective Rhodium-Catalysed Arylation of Electron-Deficient Alkenylarenes

1. Introduction

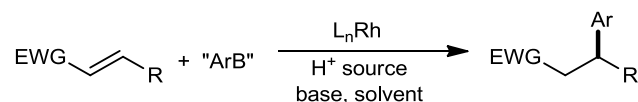
In 1987, the FDA (Food and Drug Administration, U.S.) published guidelines, followed by a policy statement in 1992, discouraging the development of racemic drugs.¹ Consequently, there has been dramatic growth in the field of transition metal-catalysed asymmetric reactions for important organic transformations.²⁻⁹ While approximately one-third of all new molecular entity approvals by the FDA were racemic during the 1980's, this figure dropped to a mere 6% between 2001 and 2007.

1,4-Nucleophilic additions are a well-established methodology in modern organic chemistry. The mechanism of a typical 1,4-addition involves the attack of a nucleophile to the electron-deficient center of an alkene conjugated to an electron-withdrawing group, such as a carbonyl (Scheme 1.1).



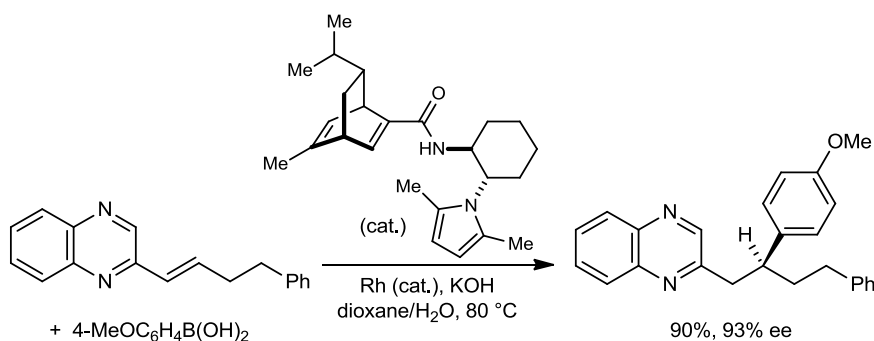
Scheme 1.1: 1,4-Nucleophilic Addition

Through this reaction method it is possible to create a stereogenic center at the β -position. Although conjugate additions are well-studied, their application in single enantiomer production through the development of new, cheap, catalytic and stereoselective processes performed under mild conditions continues to draw considerable attention.



Scheme 1.2: Simplistic Representation of Rhodium-Catalysed Hydroarylation

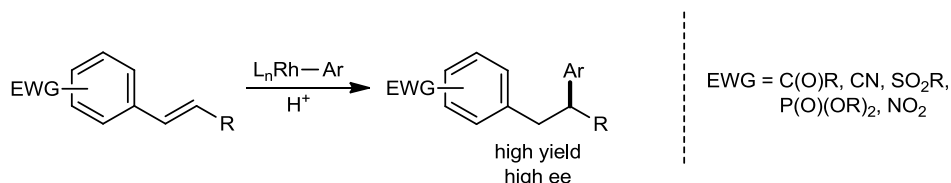
The enantioselective rhodium-catalysed 1,4-addition of arylboron compounds to β -substituted electron-deficient alkenes grants access to enantiomerically enriched compounds through the formation of a new C–C bond (Scheme 1.2).^{5, 10-15} Since the initial discovery of enones as substrates for these reactions,¹³⁻¹⁵ subsequent efforts have extended the scope of the acceptor¹⁶⁻²³ to alkenes conjugated to a range of electron-withdrawing groups.²⁴⁻⁴³ As shown in Equation 1.1, our group recently demonstrated the ability of heteroarenes containing a suitably placed C=N moiety to activate adjacent alkenes toward rhodium-catalysed asymmetric hydroarylations (RCAA).⁴³



Equation 1.1: RCAA of Alkenylheteroarenes

Our interest turned towards extending the scope of this process to include arenes containing electron-withdrawing substituents, which might provide sufficient activation

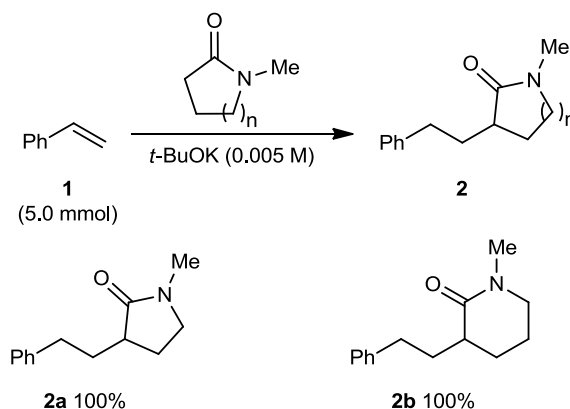
to an adjacent alkene to promote the aforementioned RCAA (Scheme 1.3). Given the ubiquitous nature of arenes in compounds for applications ranging from biology to materials science, the successful realisation of such a process would grant access to the preparation of useful molecular building blocks. A survey of related reports on conjugate addition processes are presented below.



Scheme 1.3: RCAA of Electron-Deficient Alkenylarenes

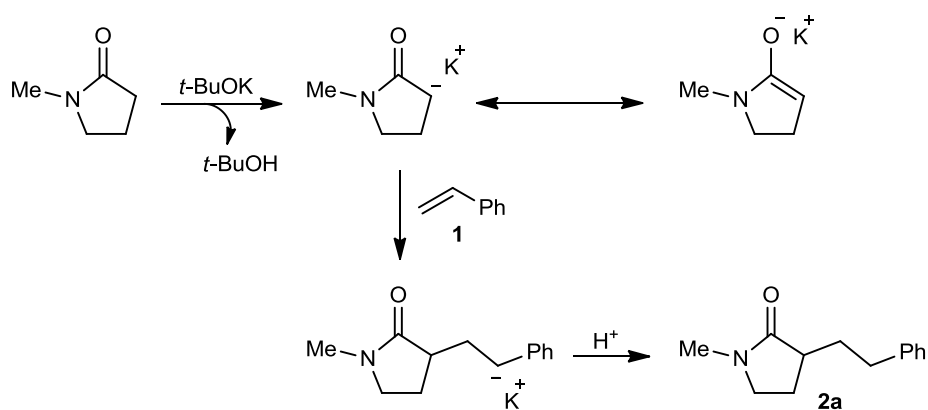
1.1. Base-Catalysed 1,4-Nucleophilic Additions to Alkenylarenes

Several base-catalysed additions to alkenylarenes have been reported previously.⁴⁴⁻⁵¹ For example, in 1970, Pines and co-workers described the base-catalysed addition of *N*-methyl-2-pyrrolidone and *N*-methyl-2-piperidone to styrene using *t*-BuOK (Scheme 1.4).⁴⁴



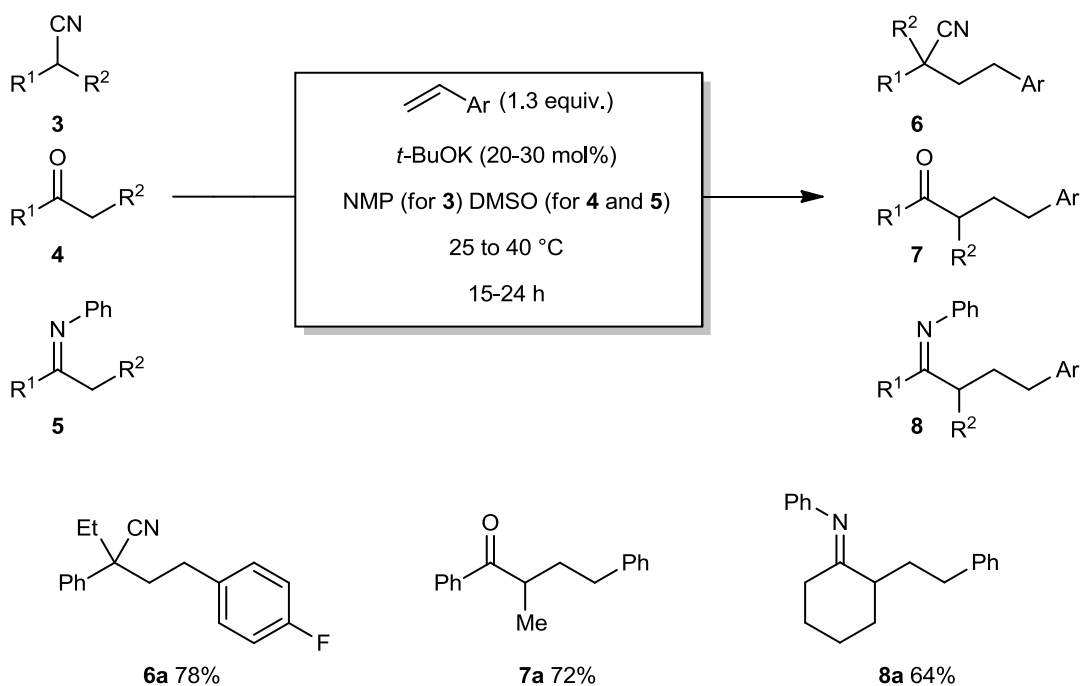
Scheme 1.4: Base-Catalysed Addition of *N*-Methyl-2-pyrrolidone or *N*-Methyl-2-piperidone to Styrene

The mechanism for this reaction as proposed by Pines is shown in Scheme 1.5.



Scheme 1.5: Mechanism for Base-Catalysed Addition of *N*-Methyl-2-Pyrrolidone to Styrene

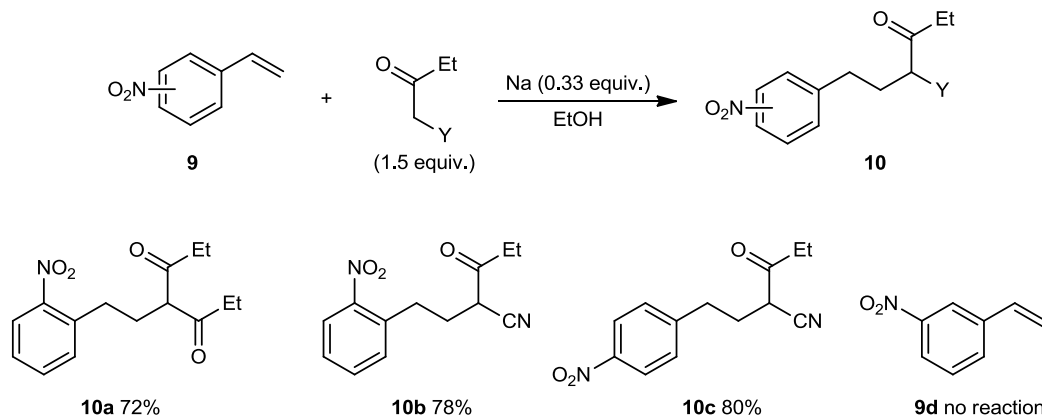
This methodology has been applied more recently by Knochel's group in the non-enantioselective addition of various alkylnitriles, alkylketones, and alkylimines to vinylarenes in the presence of sub-stoichiometric quantities of base (Scheme 1.6).⁴⁵



Scheme 1.6: Base-Catalysed Addition of Alkylnitriles, Alkylketones, and Alkylimines to Vinylarenes

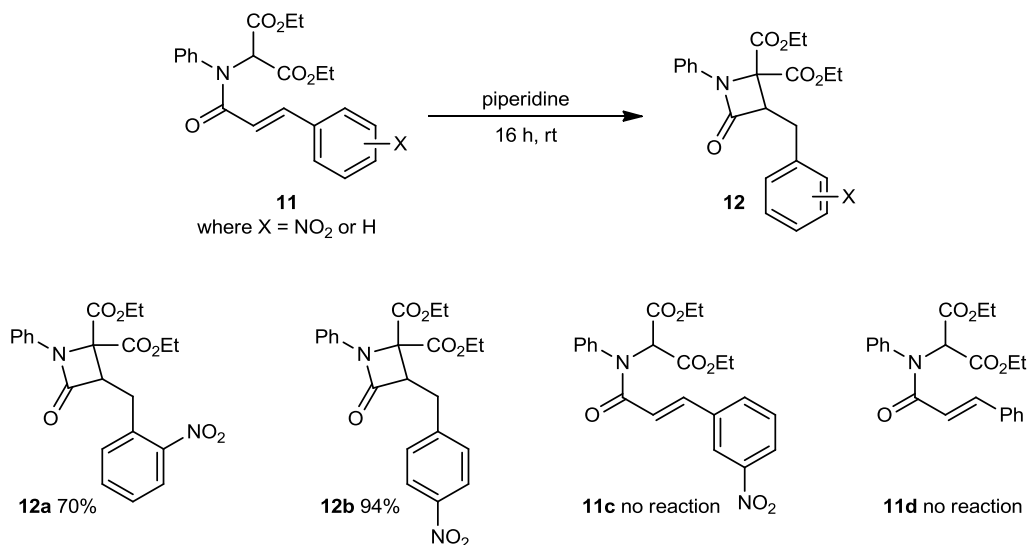
Numerous reports of strongly activated alkenylarenes undergoing similar conjugate additions exist in literature also. For example, Strobel and co-workers reported the

addition of various active methylene compounds to *o*- and *p*-nitrostyrene (Scheme 1.7).⁴⁷ *m*-Nitrostyrene **9d** failed to react. This result is not unexpected since the nitro group on the arene, in this case, is not conjugated to the adjacent alkene.



Scheme 1.7: Base-Catalysed Addition of Active Methylene Compounds to *o*- and *p*-Nitrostyrene

A similar study conducted by Bose and co-workers in 1965 demonstrated the intramolecular addition of stabilised carbon nucleophiles to alkenes conjugated to nitroarenes using piperidine as the basic solvent (Scheme 1.8).⁴⁹ The importance of the nitro group at the *o*- and *p*-positions, thus in conjugation with the adjacent alkene, is again highlighted in this report where substrates **11c** and **11d** failed to react.

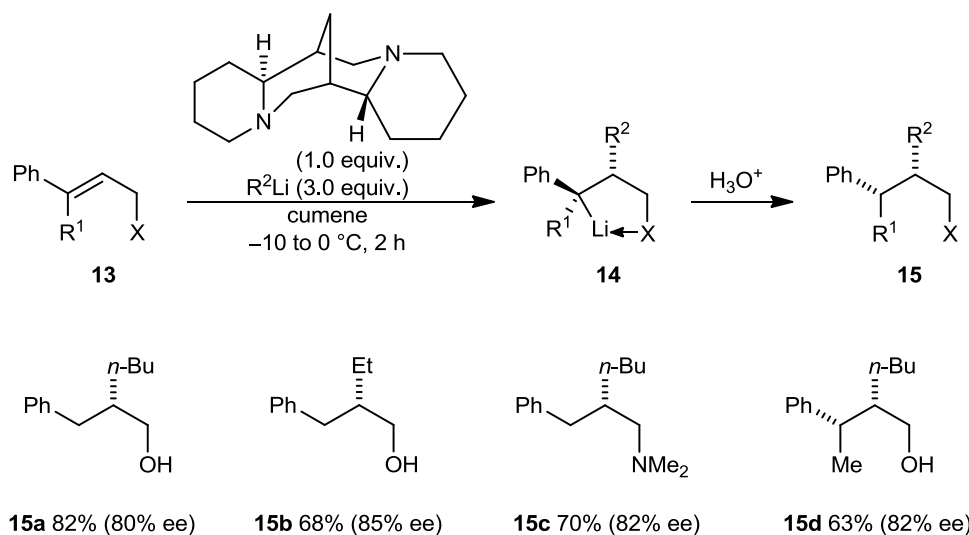


Scheme 1.8: Intramolecular Addition of Carbon Nucleophiles to Alkenyl-*p*-nitroarenes

1.2. Stoichiometric Enantioselective Carbolithiations of Alkenylarenes

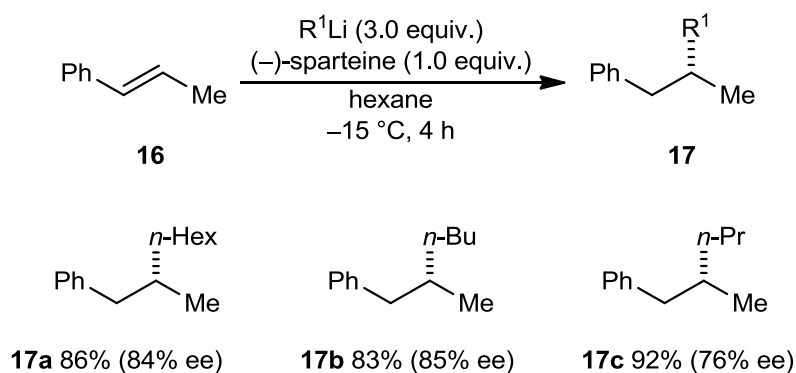
The base-catalysed conjugate additions discussed above proceed efficiently under mild conditions but do not deliver enantioenriched products. However, this has been achieved by employing highly reactive organolithium reagents.⁵²⁻⁵⁶

The asymmetric carbolithiation of cinnamyl derivatives has previously been reported by Normant and co-workers where a (–)-sparteine or (+)-sparteine surrogate was used as the chiral ligand (Scheme 1.9).⁵⁷⁻⁶⁰ Employing a trisubstituted alkene **13d** led to the formation of product **15d** possessing two stereocenters.



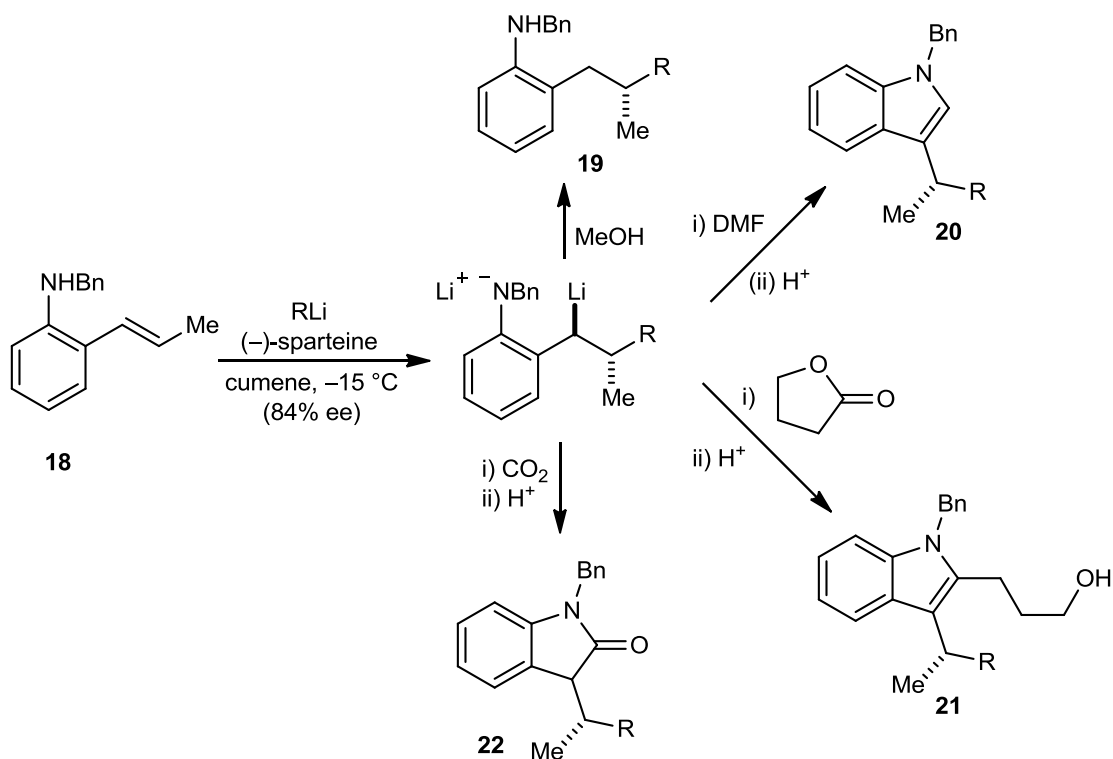
Scheme 1.9: Asymmetric Carbolithiations of Cinnamyl Derivatives in the Presence of (–)-Sparteine

It was speculated that the high stereoselectivity observed may be arising from the ability of heteroatom X on the β -linkage to donate its lone pair of electrons to lithium (as shown in species **14**). A subsequent report by the same group revealed that such an influence was not essential (Scheme 1.10).⁶¹



Scheme 1.10: Asymmetric Carbolithiations of β -Alkyl Styrenes in the Presence of (–)-Sparteine

The described carbolithiations have also been applied to *o*-substituted alkenylarene **18**, which can undergo further transformation to produce 2-alkylanilines, 3- and 2,3-substituted indoles and 3-substituted indol-2-ones with a common ee of 84% (Scheme 1.11).⁶²⁻⁶⁴

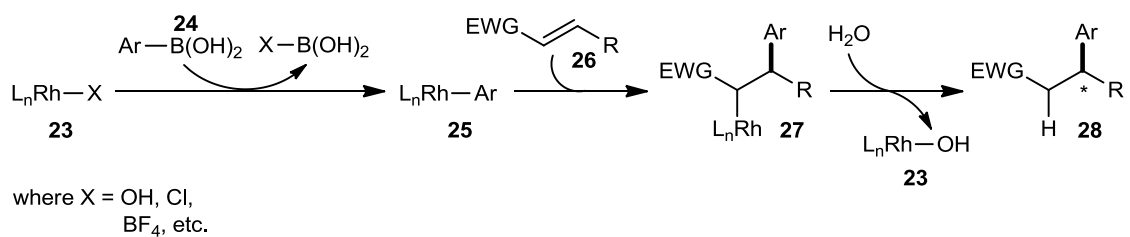


Scheme 1.11: Application of Asymmetric Carbolithiations

As discussed above, the enantioselective addition of various nucleophiles to alkenylarenes is made possible primarily through the use of highly reactive organolithium reagents that are known to exhibit low tolerance toward sensitive functional groups. Therefore, there exists a need to develop transition metal-catalysed asymmetric methodologies that are functional group-tolerant and capable of providing the desired products under mild conditions.

1.3. Rhodium-Catalysed Asymmetric Hydroarylations

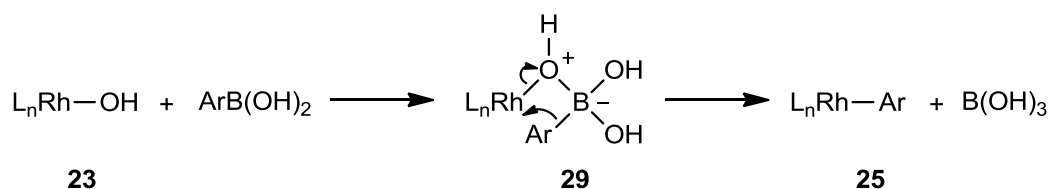
Since Miyaura's initial report on the non-enantioselective rhodium-catalysed addition of arylboronic acids to enones, numerous other RCAA have been reported to date.^{5, 10-12, 14, 65} A typical rhodium-catalysed addition of an arylboron reagent **24** to an electron-deficient acceptor **26** is believed to proceed as shown in Scheme 1.12. First, the transmetalation of an aryl group from **24** with the ligated rhodium species **23** produces the reactive aryl–rhodium species **25**. Coordination of the alkene in compound **26** with **25** and subsequent insertion into the Rh–Ar bond leads to the formation of adduct **27**, which is readily protonated under protic conditions to liberate product **28** and regenerate the rhodium species **23**.



Scheme 1.12: Rhodium-Catalysed 1,4-Arylation

The proposed mechanism for the formation of aryl–rhodium species **25** (Scheme 1.13) assumes that transmetalation from boron to rhodium proceeds through coordination of the Rh–OH complex **23** with an highly oxophilic arylboronic acid to give intermediate **29** as a quaternised boron anion, from which the aryl fragment is transferred to rhodium in an intramolecular fashion to generate the aryl–rhodium species **25** and boric acid. This transmetalation occurs under neutral conditions, but can be greatly accelerated by

the addition of a stoichiometric base. This is attributable to the quaternisation of arylboronic acid, which facilitates the rupture of the B–Ar bond.⁶⁶⁻⁶⁷



Scheme 1.13: Proposed Mechanism for the Transmetalation of Arylboronic Acids to Rhodium

The rhodium-catalysed addition of phenylboronic acid to 2-cyclohexenone, commonly known as the Hayashi-Miyaura reaction, is typically used as a model system to gauge catalytic activity of various ligands. As shown in Figure 1.1, numerous phosphine-, alkene-, nitrogen-, sulfur-, *N*-heterocyclic carbene (NHC)-based and their hybrid ligands containing two different coordinating centers have been reported to display excellent activity.⁶⁵ Bissulfoxide and NHC ligands are two new and emerging classes of ligands in RCAA. For the purposes of this paper, reports employing well-documented bisphosphine and diene ligands will be discussed primarily.

Regarding the rhodium precatalyst, $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ is the favourable choice because of its rapid and irreversible ligand exchange.¹⁴ 1,5-Cyclooctadiene (cod)-based rhodium precursors, such as $[\text{Rh}(\text{cod})\text{Cl}]_2$ and $[\text{Rh}(\text{cod})\text{OH}]_2$, are usually avoided due to their slow and reversible ligand exchange step, which in turn allows them to compete with their corresponding chiral ligated rhodium complexes in solution, thereby diminishing the observed enantioselectivity of the RCAA.^{29, 66}

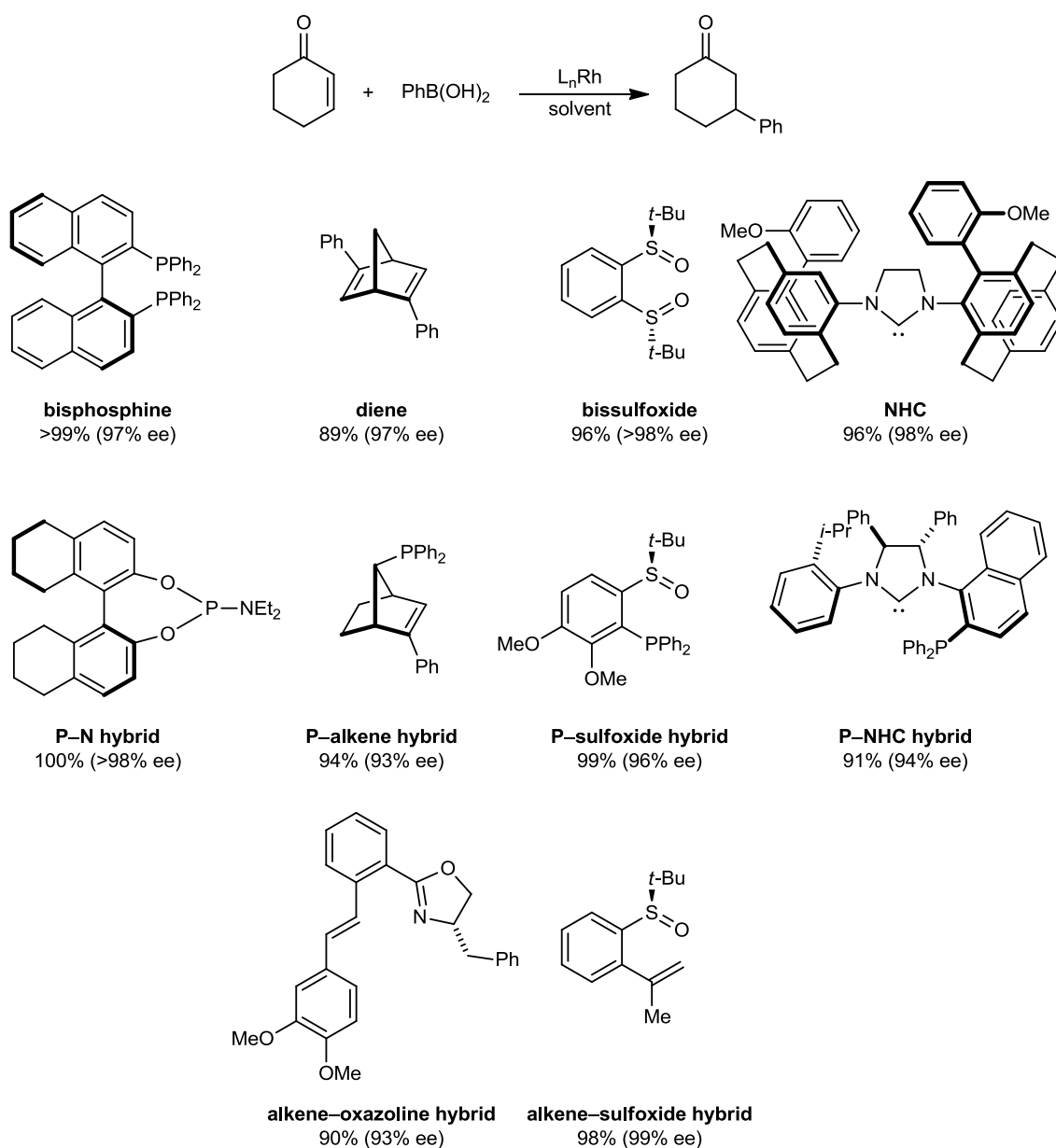


Figure 1.1: Ligand Types for RCAA

Early reports on RCAA have utilised arylboronic acids **30** as the source of the nucleophile (Figure 1.2). However, it is found that trace amounts of phenol existing in commercially available boronic acids can severely deactivate the ligated rhodium catalyst.⁶⁸ The phenol impurity can be easily removed by dehydration of the boronic acid to form the cyclic trimeric anhydride (boroxine **31**), followed by washing with hexane. The pure boroxine **31** can be readily hydrolysed back to the corresponding boronic acid **30** under basic aqueous conditions. Pinacol boronic esters **32** react slowly

in RCAA because of their sluggish hydrolysis. The additional coordination in *N*-methyliminodiacetic acid (MIDA) boronates **33** greatly improves their stability, resulting in slow release of boronic acids from MIDA boronates to keep minimal amounts of free boronic acid throughout the RCAA. The reactive ArB(9-BBN) derivatives **34** are often applied in RCAA in aprotic solvents to afford a stable chiral boron enolate in the absence of base,⁶⁹ which can be further trapped by other electrophiles to undergo tandem reactions. Other arylboron reagents include potassium aryltrifluoroborate salts **35**, lithium trimethylarylbamate salts **36**, and sodium tetraarylbamate salts **37**.

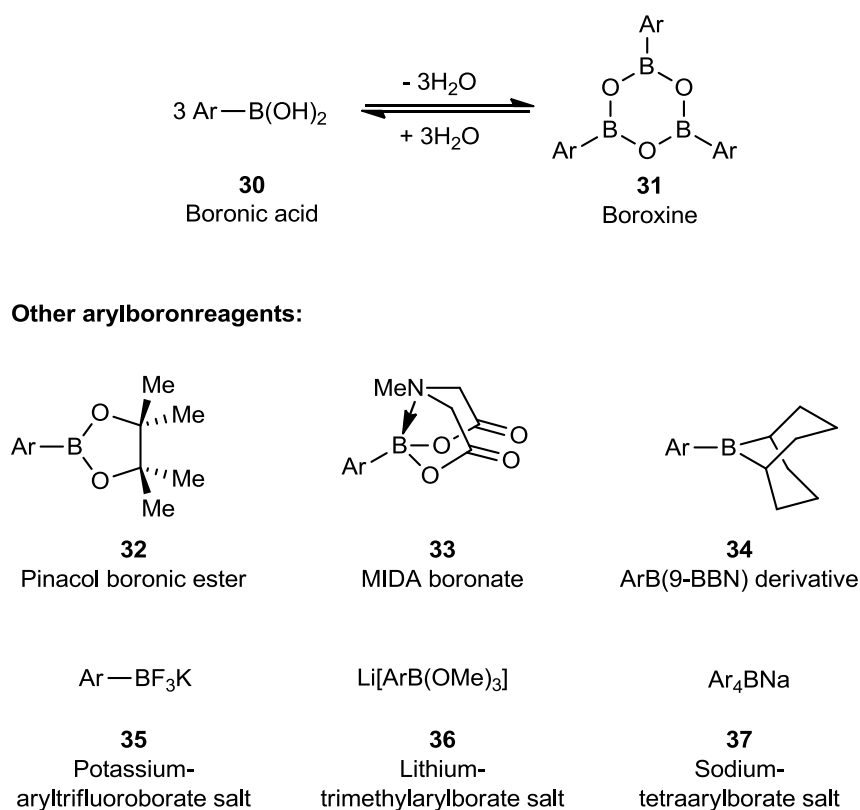
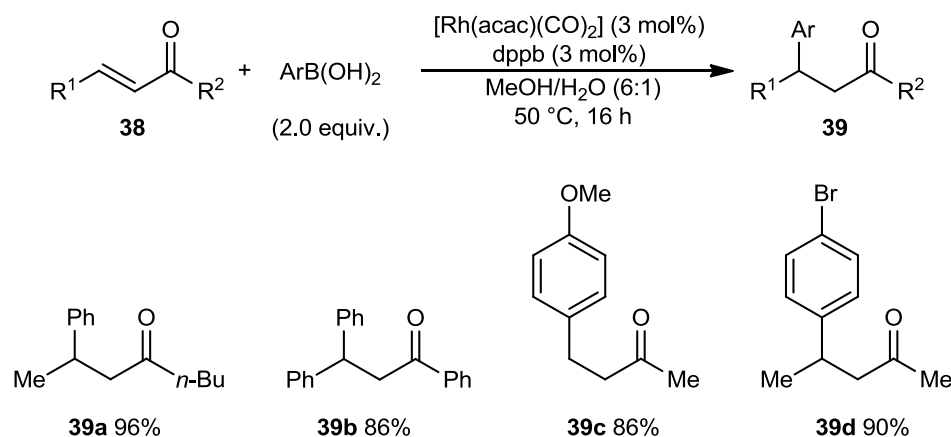


Figure 1.2: Arylboron Reagents for RCAA

Boroxines **31** are becoming one of the preferred reagents for RCAA because of the convenient addition in accurate stoichiometry and their better stability toward protodeboration than boronic acids, particularly at high temperature.

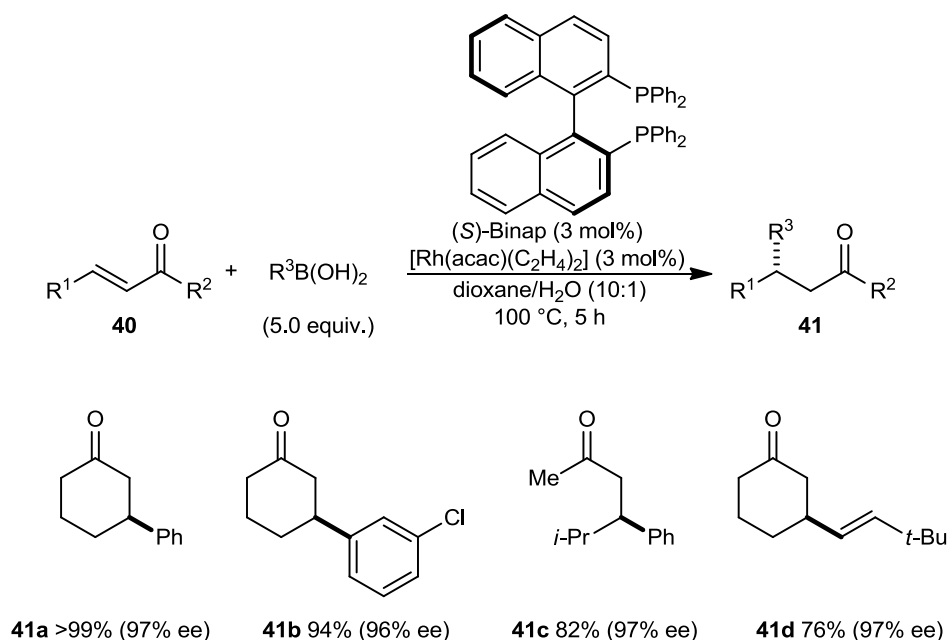
1.3.1. RCAA of α,β -Unsaturated Ketones

The first rhodium-catalysed addition of arylboronic acids to electron-deficient alkenes was described by Miyaura and co-workers in 1997.¹³ In this report, the combination of $[\text{Rh}(\text{acac})(\text{CO})_2]$ and 1,4-bis(diphenylphosphino)butane (dppb) ligand was shown to efficiently catalyse the conjugate addition of arylboronic acids to linear α,β -unsaturated ketones **38** in an aqueous co-solvent system (Scheme 1.14). The author observed no competing uncatalysed reaction of the arylboronic acids to the enones. More interesting to note is the exclusive production of the 1,4-addition product in preference to 1,2-addition. Sensitive functional groups were tolerated on the organoboron reagent (products **39c** and **39d**), which is in contrast to conjugate addition reactions that employ highly reactive organolithium and Grignard reagents. Lastly, conducting the reaction under neutral conditions in the presence of water adds to the merit of this methodology.



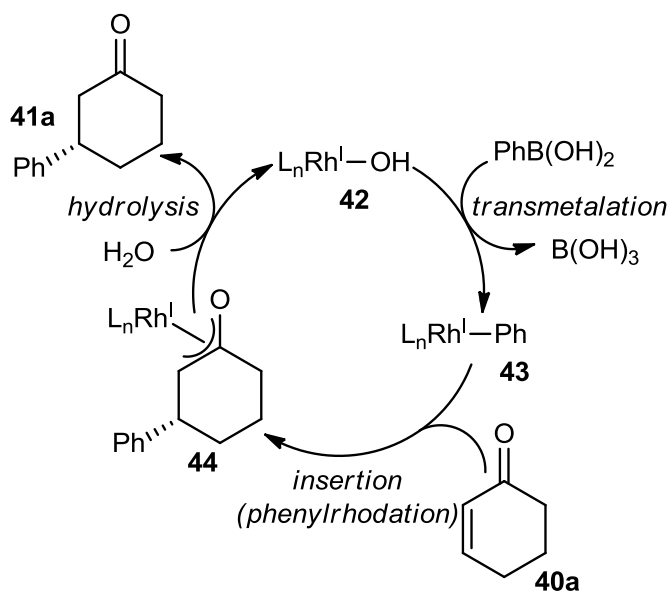
Scheme 1.14: Rhodium-Catalysed Hydroarylation of Enones

A year later, Hayashi and Miyaura developed the asymmetric variant to this process by employing a chiral bisphosphine-ligated rhodium catalyst (Scheme 1.15).¹⁴ The conjugate addition to cyclic and acyclic ketones proceeded with high conversion and excellent enantioselectivity. Addition of an alkenylboronic acid was also possible affording **41d** in 76% isolated yield.



Scheme 1.15: RCAA of Enones

In 2002, Hayashi and co-workers presented a detailed mechanism for the Hayashi-Miyaura reaction (Scheme 1.16).¹⁵ According to the report, the reaction is initiated through the transmetalation of a phenyl group from boron to hydroxorhodium **42** to generate the phenyl–rhodium species **43**. Subsequently, 2-cyclohexenone **40a** inserts into the Rh–Ph bond of **43** to form the oxa- π -allylrhodium **44**, which is unstable under protic conditions and readily hydrolysed to regenerate **42** and liberate the RCAA product **41a**. It is noteworthy that rhodium remains at a constant oxidation state of +1 throughout the catalytic cycle. Through detailed kinetic studies, Hayashi and co-workers were also able to reveal that the transmetalation from boron to rhodium was the rate-determining step in the catalytic cycle.

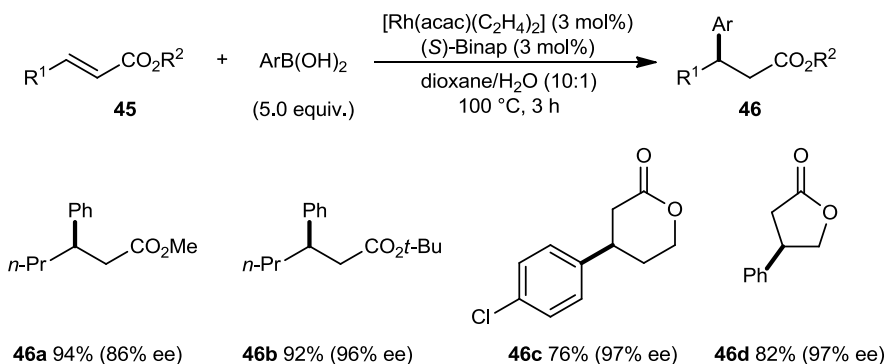


Scheme 1.16: Catalytic Cycle for the Hayashi-Miyaura Reaction

Since Hayashi's early report on the RCAA of enones, various electron-withdrawing groups other than a ketone have also been shown to activate adjacent alkenes toward RCAA.

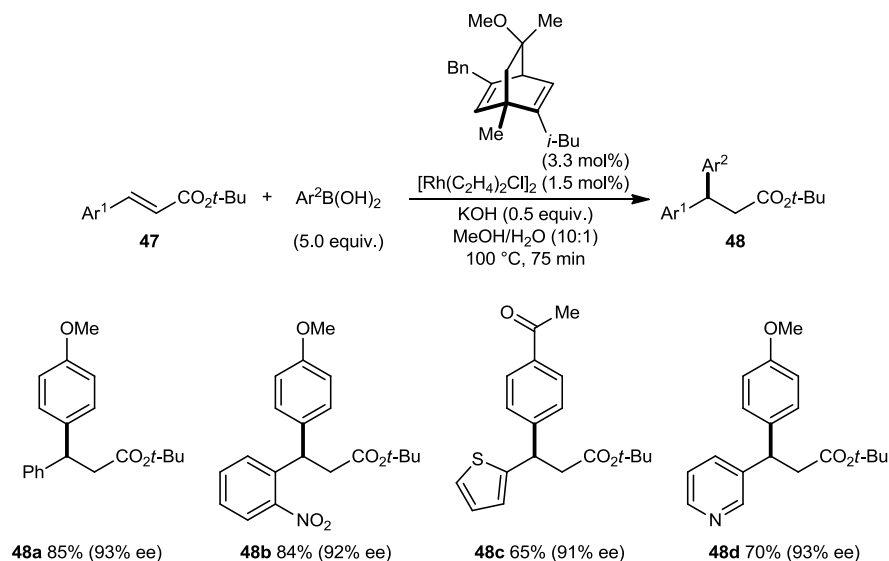
1.3.2. RCAA of α,β -Unsaturated Esters

As shown in Scheme 1.17, linear and cyclic enoates served as suitable candidates for RCAA.²⁴⁻²⁵



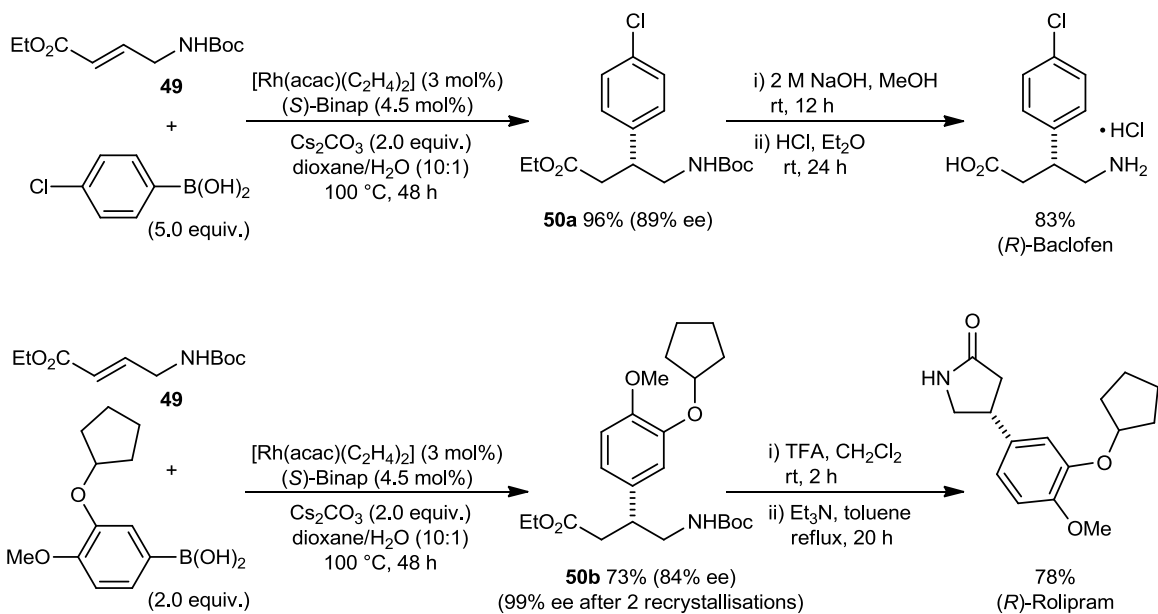
Scheme 1.17: RCAA of Enoates Using a Chiral Bisphosphine Ligand

In 2005, Carreira showed that a chiral diene-ligated rhodium catalyst could be used for the RCAA of β -aryl enoates (Scheme 1.18).²⁶ A strongly electron-withdrawing nitro group at the sterically demanding *o*-position of the arene ring of substrate **47b** did not hinder the reaction. The system could also tolerate heteroaromatic β -substituents as evidenced from the smooth arylation of substrates **47c** and **47d**.



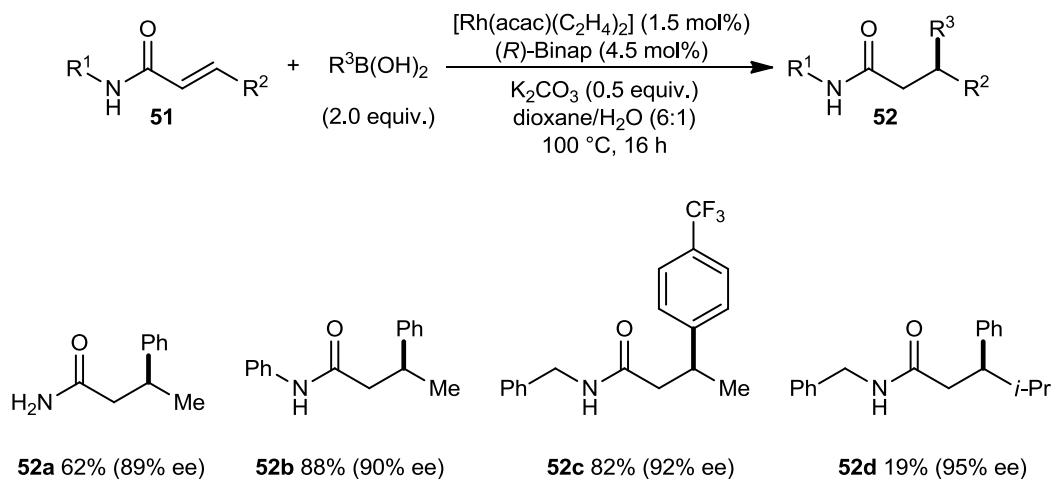
Scheme 1.18: RCAA of β -Aryl Enoates Using a Chiral Diene Ligand

The RCAA of linear enoates was applied by Helmchen and co-workers toward the synthesis of (*R*)-Baclofen, which is an agonist for the GABA_B receptors; and (*R*)-Rolipram, which is a selective phosphodiesterase inhibitor (Scheme 1.19).²⁷

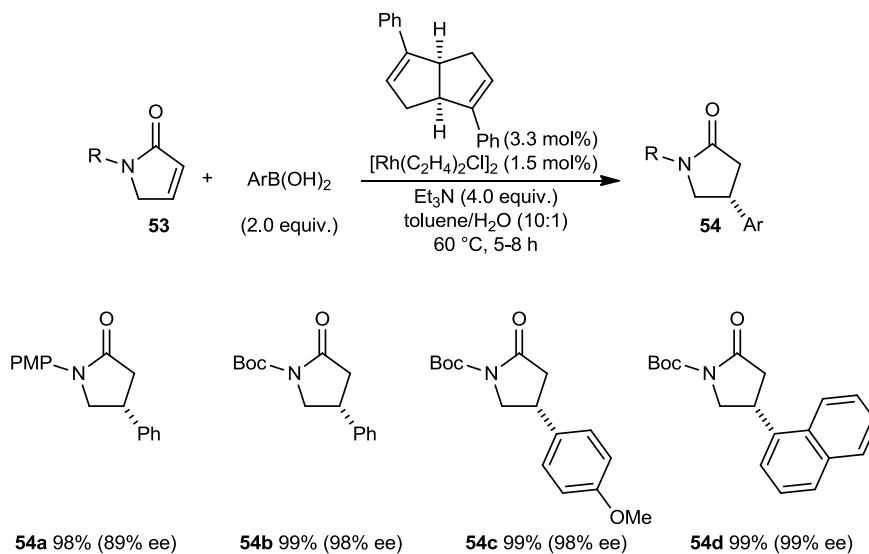


1.3.3. RCAA of α,β -Unsaturated Amides

In 2001, Miyaura and co-workers reported the RCAA of linear α,β -unsaturated amides (Scheme 1.20).²⁹



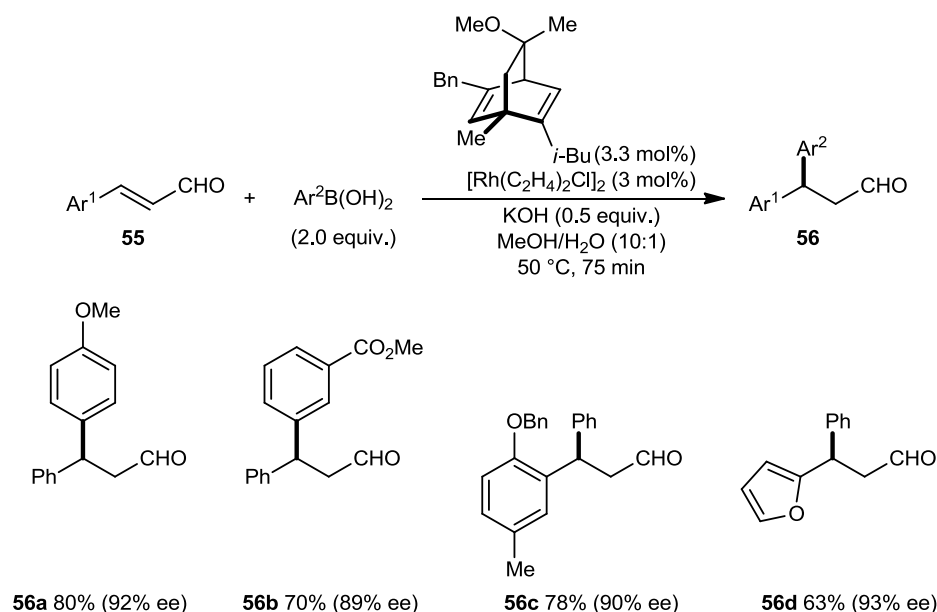
More recently, Lin and co-workers have described the highly enantioselective rhodium-catalysed hydroarylation of cyclic α,β -unsaturated amides to afford β -substituted- γ -lactams (Scheme 1.21).³¹



Scheme 1.21: RCAA of Cyclic α,β -Unsaturated Amides

1.3.4. RCAA of α,β -Unsaturated Aldehydes

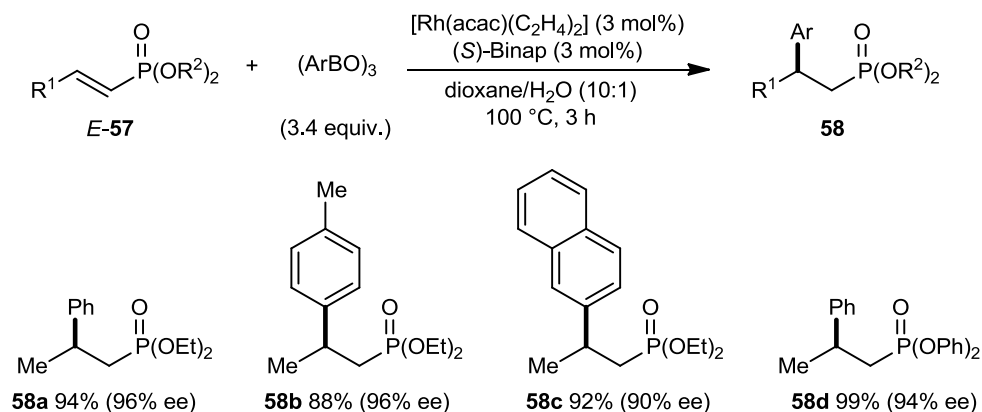
In 2005, Carreira and co-workers successfully performed the RCAA of enals using a chiral diene ligand (Scheme 1.22).³² The RCAA of enals **55** presents a special challenge due to the high reactivity of aldehydes and their propensity to undergo 1,2-addition. Remarkably, the catalytic system developed by Carreira and co-workers was highly selective and solely produced the 1,4-addition products **56** while leaving the aldehyde intact, despite the use of an excess amount of the arylboronic acid.



Scheme 1.22: RCAA of β -Aryl Enals

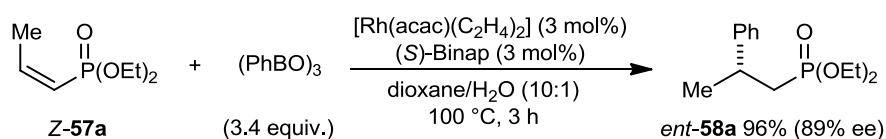
1.3.5. RCAA of α,β -Unsaturated Phosphonates

α,β -Unsaturated phosphonates can also undergo RCAA, as demonstrated by Hayashi and co-workers by making use of a chiral bisphosphine-ligated rhodium complex (Scheme 1.23).³³ Arylboroxines were found to be better suited for these substrates than arylboronic acids, since product **58a** was produced in a low 44% yield and an 84% ee when phenylboronic acid was employed under otherwise similar conditions.



Scheme 1.23: RCAA of α,β -Unsaturated Phosphonates

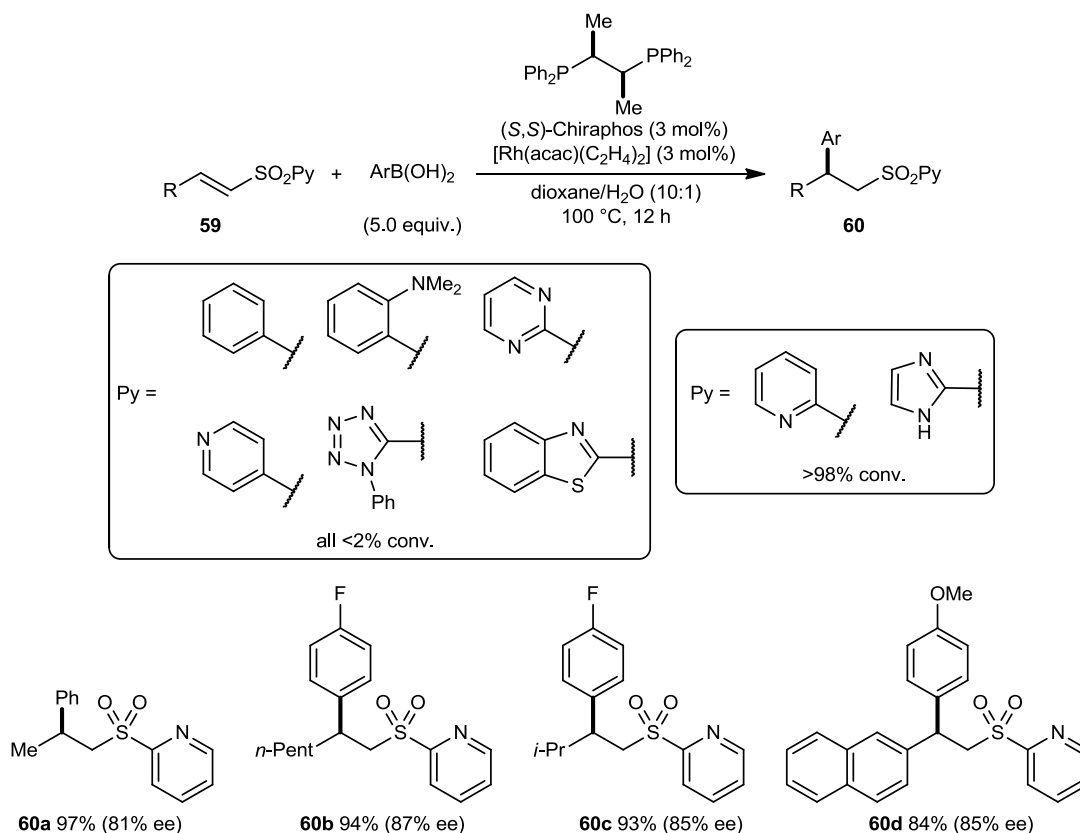
Consistent with the stereochemical model, the *trans* and *cis* geometries of alkenylphosphonate **57a** afforded opposite enantiomers (Equation 1.2).



Equation 1.2: Stereochemical Outcome for RCAA of α,β -Unsaturated Phosphonates

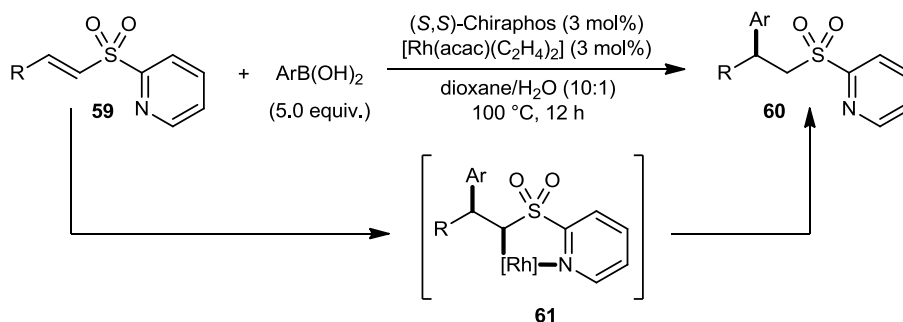
1.3.6. RCAA of α,β -Unsaturated Pyridylsulfones

Alkenyl-2-pyridylsulfones have also been shown to participate in RCAA (Scheme 1.24).³⁴⁻³⁶ Interestingly, a range of α,β -unsaturated (hetero)arylsulfones were found to be poor candidates for RCAA. However, α,β -unsaturated *o*-pyridylsulfones underwent conjugate arylations to afford products **60** in high yields and enantioselectivities.



Scheme 1.24: RCAA of α,β -Unsaturated Pyridylsulfones

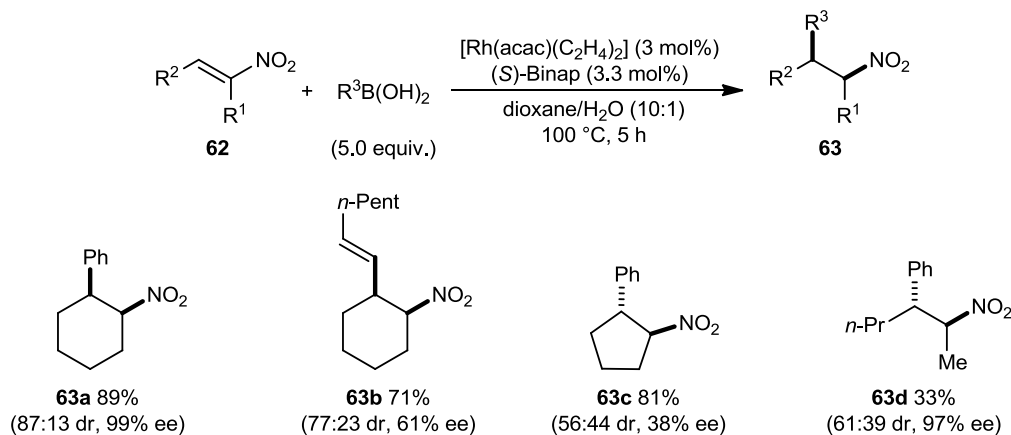
The report suggested that the unique position of the nitrogen at the *o*-position of the pyridylsulfone may help to stabilise the rhodium complex **61** formed during the reaction (Scheme 1.25).



Scheme 1.25: Importance of 2-Pyridyl Group in RCAA of α,β -Unsaturated Pyridylsulfones

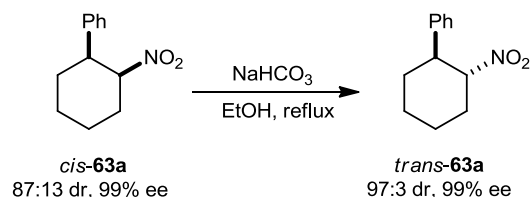
1.3.7. RCAA of Nitroalkenes

Hayashi and co-workers have also demonstrated the use of nitroalkenes as strong acceptors in RCAA (Scheme 1.26).³⁷ While the addition of arylboronic acids to 6-membered cyclic nitroalkenes gave the arylated product in high diastereo- and enantioselectivity (product **63a**), there was a significant loss in diastereo- and/or enantioinduction when switching to alkenyl boronic acids (product **63b**), to 5-membered cyclic nitroalkenes (product **63c**) or to acyclic nitroalkenes (product **63d**).



Scheme 1.26: RCAA of Nitroalkenes

The *cis*- β -aryl substituted cyclic nitroalkanes could easily be converted to the more thermodynamically stable *trans*-isomer by treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol (Equation 1.3).

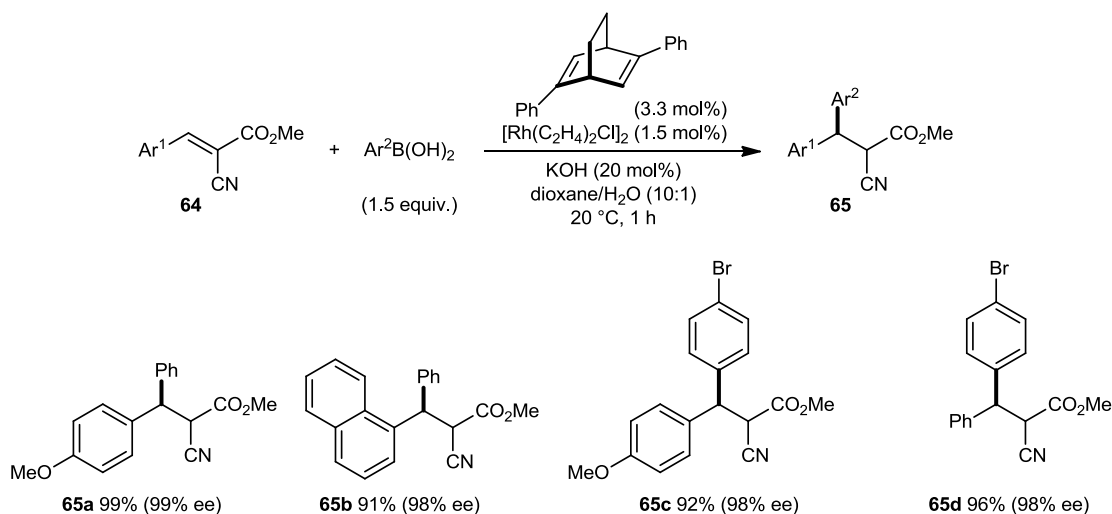


Equation 1.3: Conversion from *cis*- to *trans*- Isomer

RCAA of electron-deficient α,α -disubstituted alkenes are rare in literature, presumably due to the high steric congestion at the α -position of such substrates. Notably, Hayashi's report is one of the few examples where α,α -disubstituted alkenes underwent RCAA.

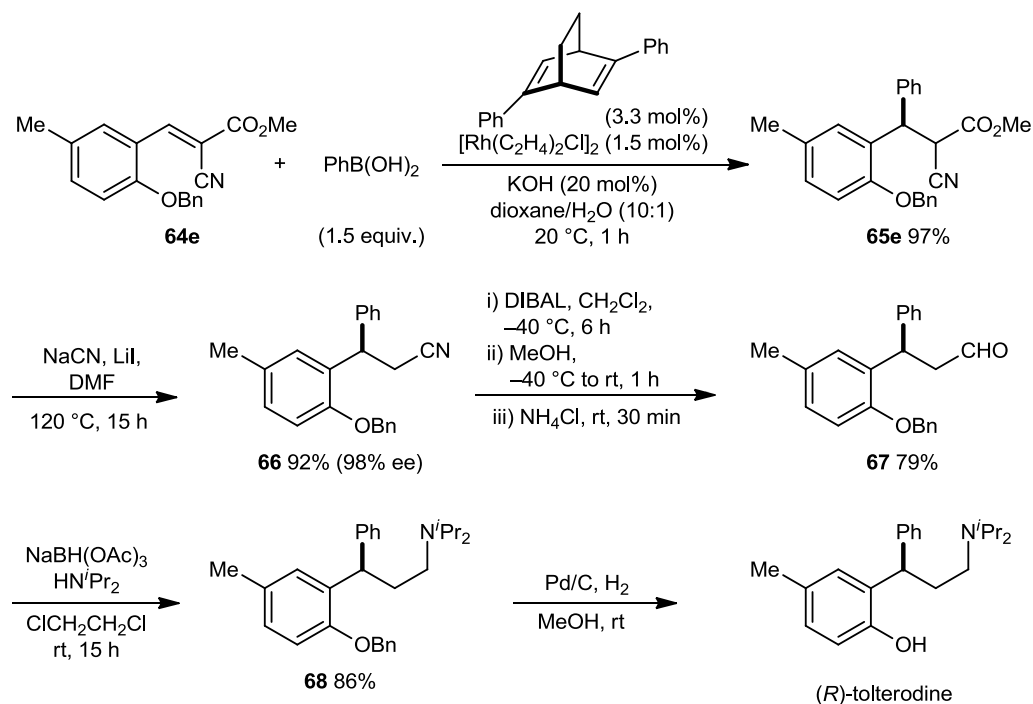
1.3.8. RCAA of Arylmethylene Cyanoacetates

In 2008, Hayashi and co-workers reported the RCAA of arylmethylene cyanoacetates **64**, which is another example of rhodium-catalysed arylations of α,α -disubstituted alkenes (Scheme 1.27).⁴⁰



Scheme 1.27: RCAA of Arylmethylene Cyanoacetates

The methodology was also applied toward the enantioselective synthesis of (*R*)-tolterodine (Scheme 1.28), which involved the rhodium-catalysed asymmetric addition of phenylboronic acid to a methylene cyanoacetate **64e** bearing a protected 2-hydroxy-5-methylphenyl group to afford the arylated product **65e**. Removal of the carbomethoxy group by treatment with NaCN and LiI in DMF gave the nitrile **66** in high enantiopurity. The cyano group was then converted to the corresponding aldehyde **67**, and subsequent reductive amination with diisopropylamine and sodium triacetoxyborohydride gave the protected tolterodine precursor **68**. Deprotection of **68** via hydrogenolysis provided the desired product in quantitative yield. (*R*)-Tolterodine is an antimuscarinic drug that is used to treat urinary incontinence.⁷⁰

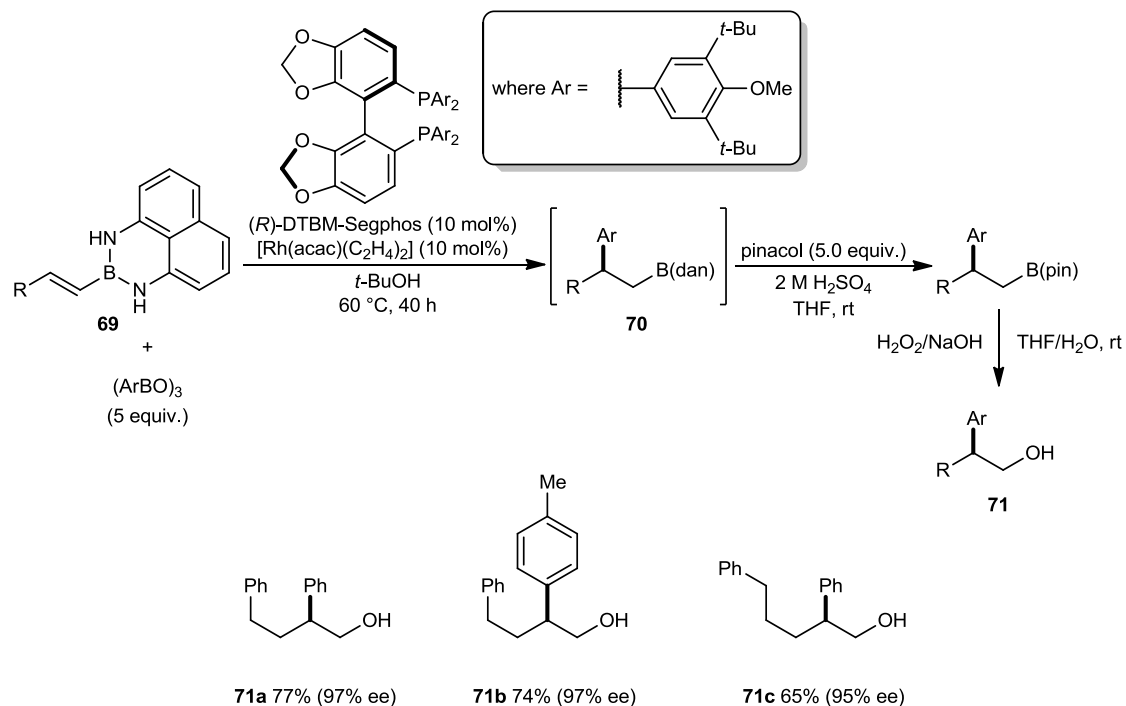


Scheme 1.28: Enantioselective Synthesis of (*R*)-Tolterodine

1.3.9. RCAA of Borylalkenes

More recently, Hayashi and co-workers have employed borylalkenes in RCAA to give chiral β -arylalkylboranes with high enantioselectivities (Scheme 1.29).⁴¹⁻⁴² The utility of

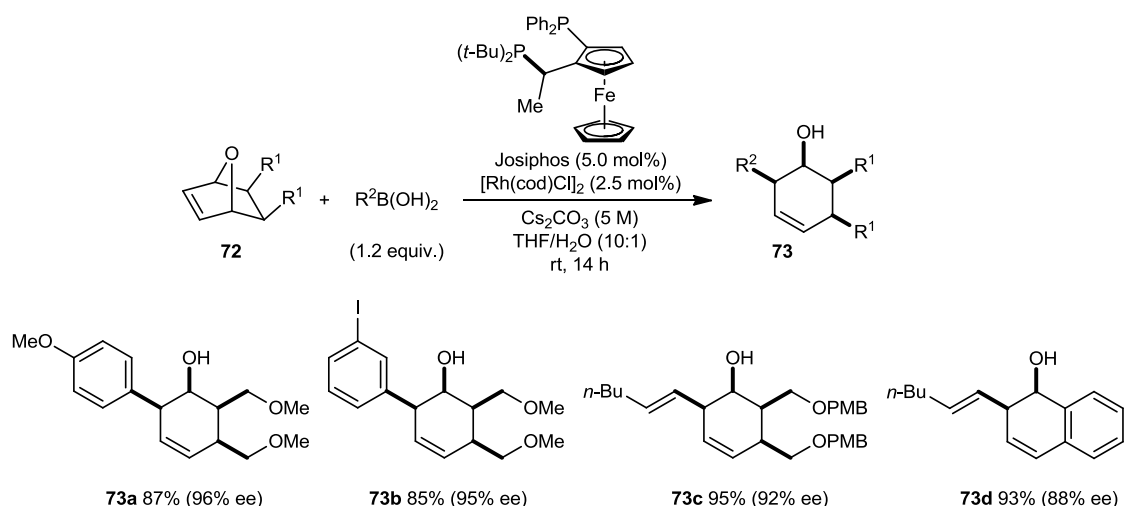
this process was demonstrated by converting the arylated boranes **70** into their corresponding alcohols **71**.



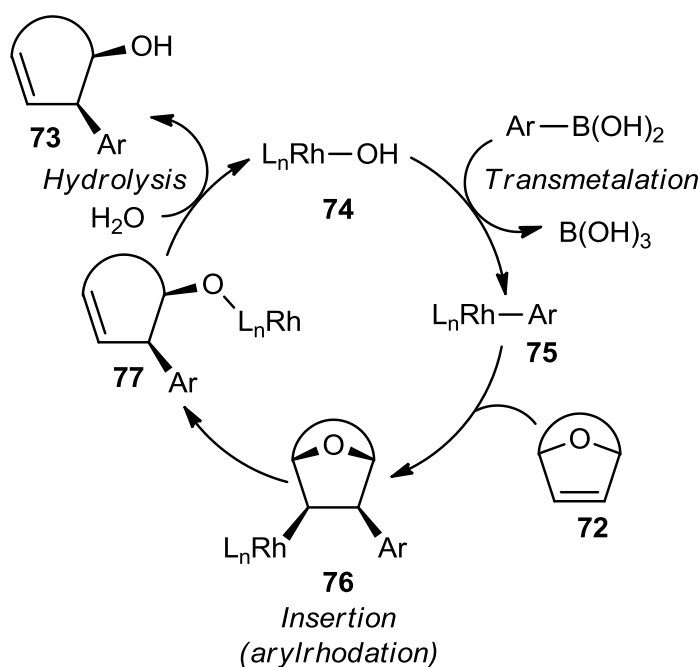
Scheme 1.29: RCAA of Borylalkenes

1.3.10. RCAA of Strained Alkenes

In 2002, Lautens and co-workers reported the rhodium-catalysed asymmetric ring opening of oxabicyclic alkenes with arylboronic acids (Scheme 1.30).¹⁷ Unlike typical RCAA where alkenes are activated through conjugation with an electron-withdrawing group, Lautens' work relied on the placement of an alkene in a strained ring system, which provided the driving force for rhodium-catalysed asymmetric arylations. Also, in a typical RCAA the carbo-rhodation step is followed by hydrolysis, whereas in this report the carbo-rhodated species underwent β -elimination instead, providing secondary alcohol-containing products with high levels diastereo- and enantiocontrol.



Scheme 1.30: Rh-Catalysed Asymmetric Arylation of Oxabicyclic Alkenes



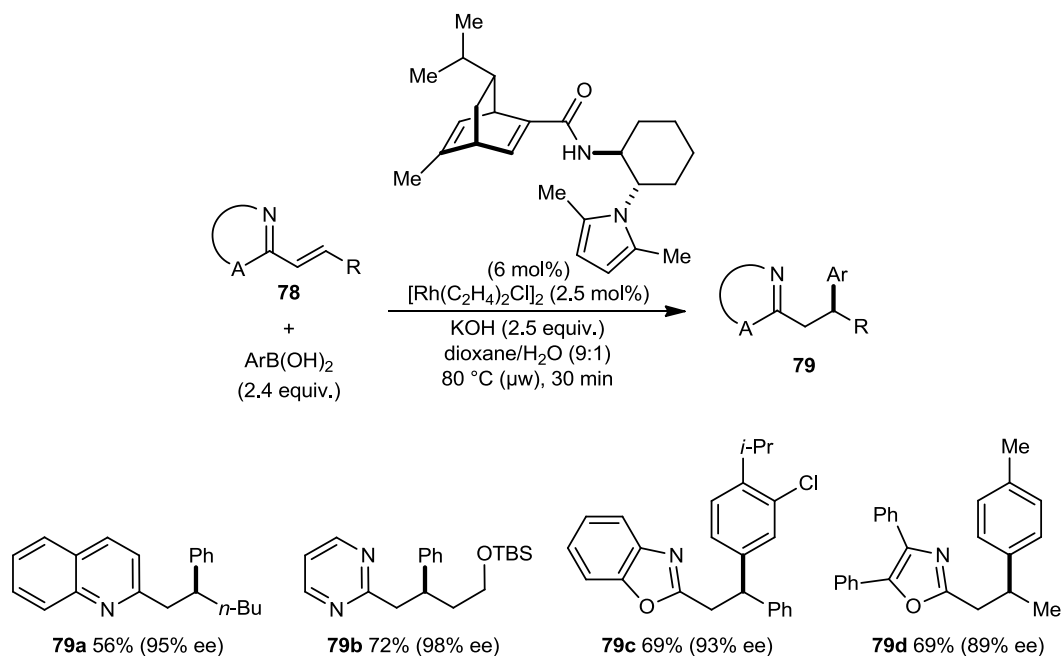
Scheme 1.31: Catalytic Cycle for the Asymmetric Ring Opening of Oxabicyclic Alkenes

The first step in the proposed mechanism for the asymmetric ring opening of oxabicyclic alkenes involves transmetalation of the arylboronic acid to ligated rhodium(I) hydroxide **74** generating intermediate **75** (Scheme 1.31). This species then undergoes an *exo*-selective asymmetric carbo-rhodation at the oxabicyclic olefin **72** to generate intermediate **76**. Chelation of the olefin and the oxygen atom of the oxabicyclic may help

to contribute to the high *exo* selectivity. β -Elimination of oxygen to give the ring-opened intermediate **77** then occurs, followed by hydrolysis to liberate the ring-opened product **73** and regenerating the ligated rhodium(I) hydroxide **74**.

1.3.11. RCAA of Alkenylheteroarenes

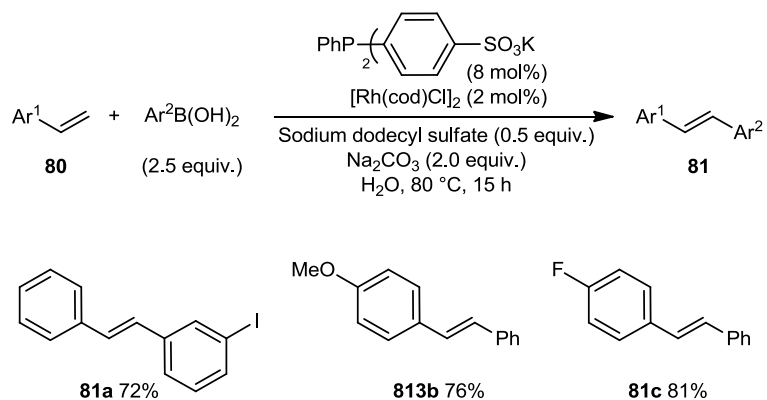
In 2010, our group demonstrated the use of C=N-containing heteroarenes for activating adjacent alkenes toward RCAA (Scheme 1.32).⁴³ In this report, the parent 2-alkenylpyridine failed to participate in RCAA; however, 2-alkenylazaarenes containing more electron-withdrawing azines (products **79a** and **79b**) and azoles (products **79c** and **79d**) successfully participated in RCAA.



Scheme 1.32: RCAA of 2-Alkenylheteroarenes

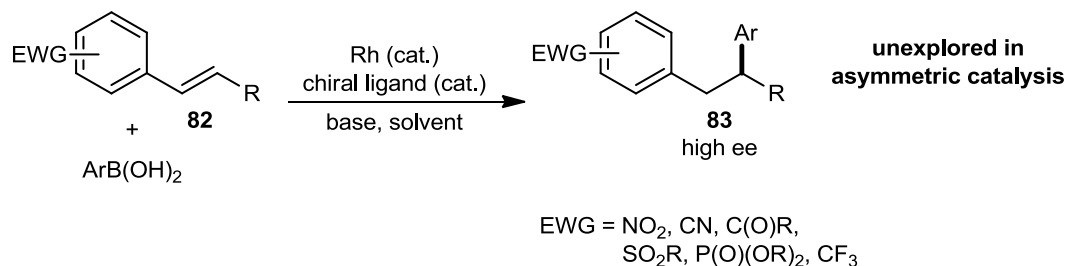
1.3.12. RCAA of Alkenylarenes

Lautens and co-workers have also shown that various vinylarenes, where activation of the adjacent alkene is minimal, can undergo rhodium-catalysed Heck-type reactions under aqueous conditions using water-soluble phosphine ligands (Scheme 1.33).⁷¹



Scheme 1.33: Rh-Catalysed Heck-Type Reaction to Vinylarenes

Drawing from past knowledge of 2-alkenylazaarenes that effectively underwent RCAA, it occurred to us that placement of a strong electron-withdrawing group (such as a nitro group) on the arene might lead to sufficient polarisation of the adjacent alkene to the point where conjugate addition products, rather than Heck-type products, would form (Scheme 1.34).

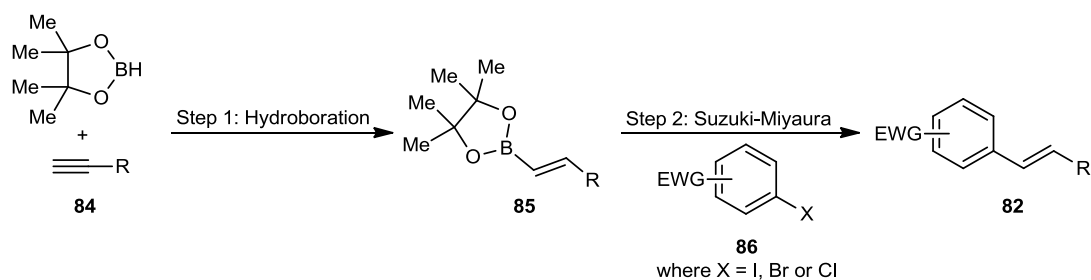


Scheme 1.34: RCAA to Electron-Deficient Alkenylarenes

Although nitroalkenes have been successfully employed in a myriad of additions of carbon nucleophiles,^{37-39, 72-74} the analogous reactions of their phenylogous counterparts **82** are extremely rare,^{18c-h} and no asymmetric reactions have been reported. Therefore, the successful realisation of the RCAA of electron-deficient alkenylarenes was an attractive goal and would set the stage for the use of this underexploited class of electrophiles in other catalytic enantioselective addition reactions.

2. Results and Discussion

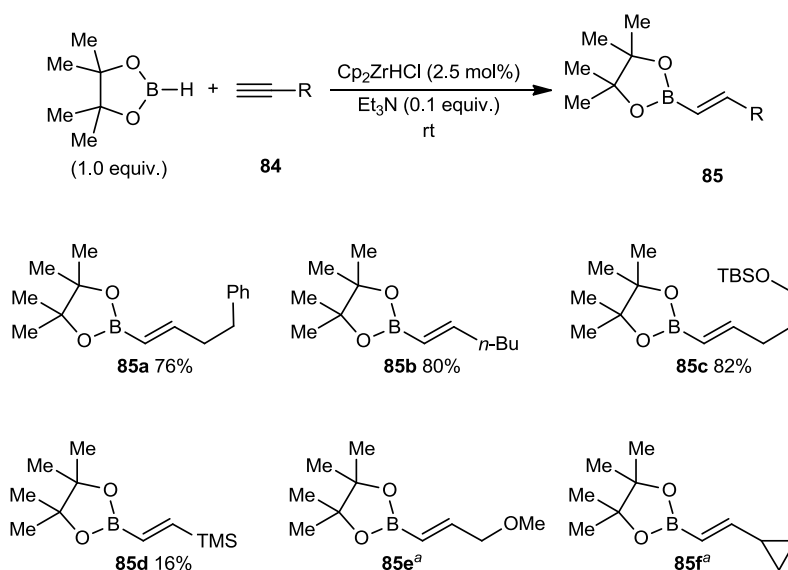
In order to test our hypothesis illustrated in Scheme 1.34, synthesis of the appropriate substrates was necessary (Scheme 1.35). In most cases, our approach comprised of a two-step strategy involving the zirconium-catalysed hydroboration of terminal alkynes **84** leading to the stereoselective production of *E*-alkenylboronic esters **85**, which were then subjected to Suzuki-Miyaura coupling conditions with aryl halides **86** containing various electron-withdrawing substituents to afford the desired substrates **82** available for RCAA chemistry.



Scheme 1.35: Strategy for the Synthesis of Alkenylarene Substrates

2.1. Step 1: Zirconium-Catalysed Preparation of *E*-Alkenylboronic Acid Pinacol Esters

For the preparation of alkenylboronic acid pinacol esters **85**, a stereoselective zirconium-catalysed procedure developed previously by Wang and co-workers was followed (Scheme 1.36).⁷⁵ The preparation of **85a-85d** proved to be fairly straightforward and the products were generally isolated in high yields.

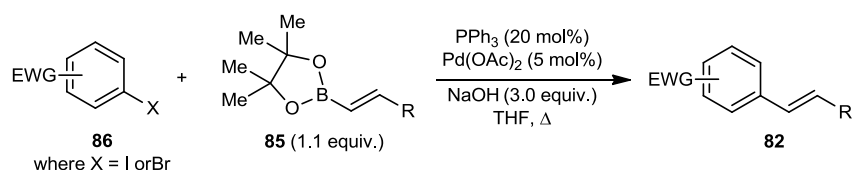


^a Reagent was purchased from commercial sources.

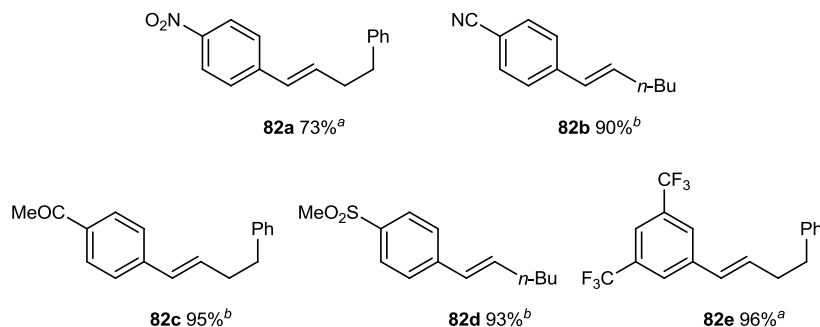
Scheme 1.36: Preparation of *E*-Alkenylboronic Esters

2.2. Step 2: Preparation of Alkenylarenes via Suzuki-Miyaura Cross-Couplings

Compounds **85a-85d** and other commercially available alkenylboronic acid pinacol esters were then coupled with a range of aryl halides **86** following standard Suzuki-Miyaura cross-coupling methodology. First, alkenylarenes containing various electron-withdrawing groups on the arene moiety were prepared (Scheme 1.37A).



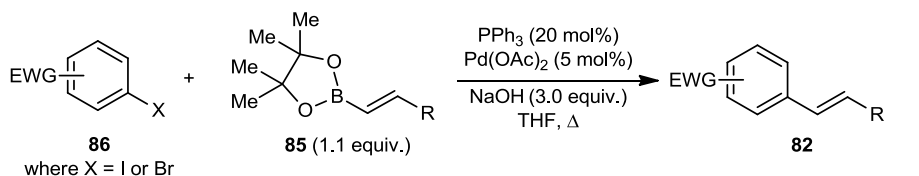
Variable Electron-Withdrawing Groups on Arene:



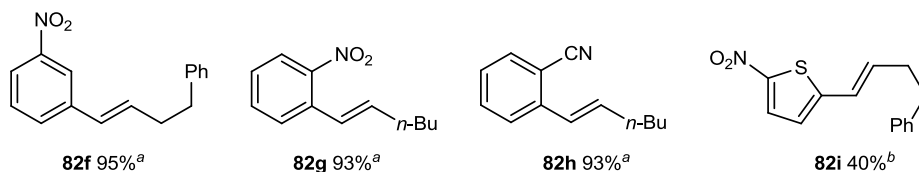
^a Reaction was conducted using aryl iodide **86**. ^b Reaction was conducted using aryl bromide **86**.

Scheme 1.37A: Preparation of Alkenylarenes

Next, strongly electron-withdrawing groups were placed at the *m*- or *o*-position of the arene (Scheme 1.37B). A 2-alkenyl-5-nitrothiophene (substrate **82i**) was also prepared.



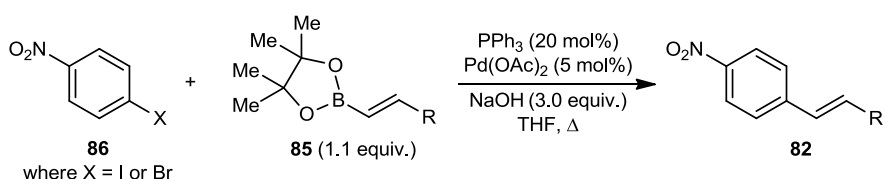
Variable Position of Electron-Withdrawing Group on Arene:



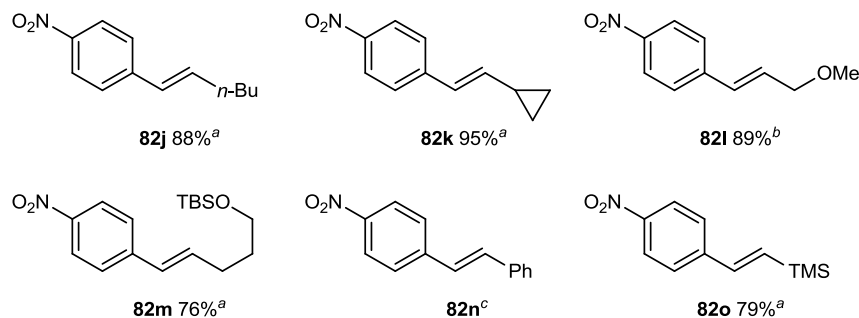
^a Reaction was conducted using aryl iodide **86**. ^b Reaction was conducted using aryl bromide **86**.

Scheme 1.37B: Preparation of Alkenylarenes

Alkenylarenes containing various β -substituents such as linear or bulky aliphatic groups (products **82j** and **82k**, respectively), an allyl ether (product **82l**), a silyl ether (product **82m**) and a trimethylsilyl group (product **82o**) were prepared (Scheme 1.37C).



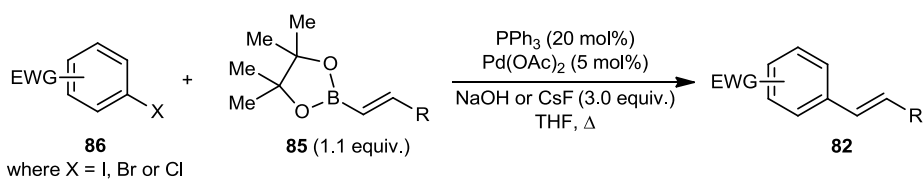
Variable β -Substituents:



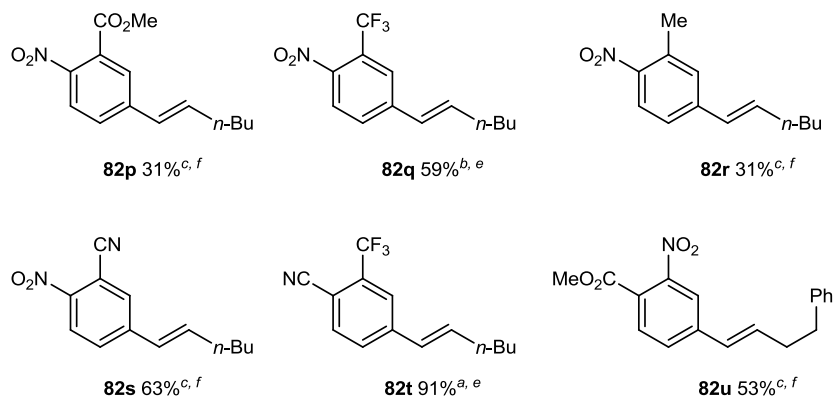
^a Reaction was conducted using aryl iodide **86**. ^b Reaction was conducted using aryl bromide **86**. ^c Reagent was purchased from commercial sources.

Scheme 1.37C: Preparation of Alkenylarenes

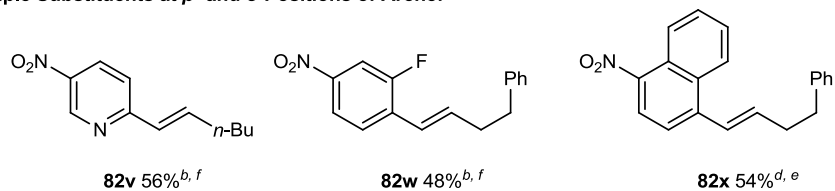
Alkenylarenes possessing *p*- and *m*-substituents (**82p-u**) or *p*- and *o*-substituents (**82v-x**) on the arene were synthesised as well (Scheme 1.37D). Generally, the desired alkenylarenes were produced in good yield. In certain cases where the arene contained more than one electron-withdrawing group, decomposition of starting material was observed. This was attributed to a side nucleophilic aromatic substitution (S_NAr) reaction that may be occurring during the coupling reaction (Equation 1.4). This was overcome by making use of a milder base such as caesium fluoride, which allowed isolation of the desired product, albeit in lower yield.



Multiple Substituents at *p*- and *m*-Positions of Arene:

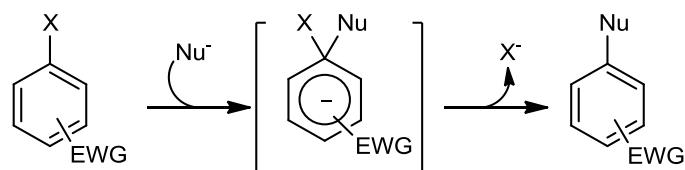


Multiple Substituents at *p*- and *o*-Positions of Arene:



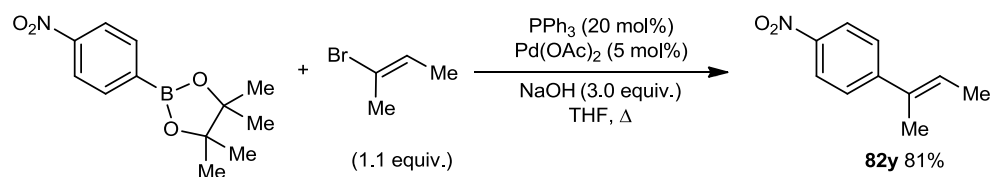
^a Reaction was conducted using aryl iodide **86**. ^b Reaction was conducted using aryl bromide **86**. ^c Reaction was conducted using aryl chloride **86**. ^d Reaction was conducted using aryl triflate **86**. ^e Reaction was conducted using NaOH. ^f Reaction was conducted using CsF.

Scheme 1.37D: Preparation of Alkenylarenes



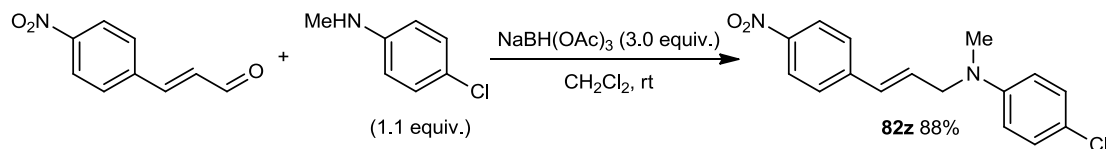
Equation 1.4: S_NAr Mechanism

α,α -Disubstituted alkenyl-*p*-nitroarene **82y** was prepared by coupling 4-nitrophenylboronic acid pinacol ester with 2-bromo-2-butene (Equation 1.5).



Equation 1.5: Preparation of α,α -Disubstituted Alkenylarenes

Lastly, alkenyl-*p*-nitroarene **82z** containing an allyl amine β -substituent was also prepared through a reductive amination (Equation 1.6).

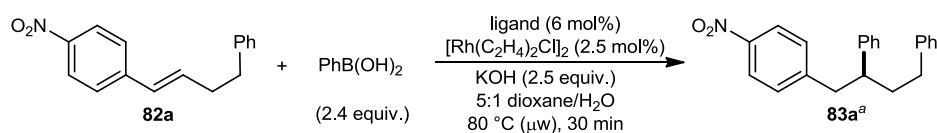


Equation 1.6: Preparation of Alkenylarenes Containing an Allyl Amine

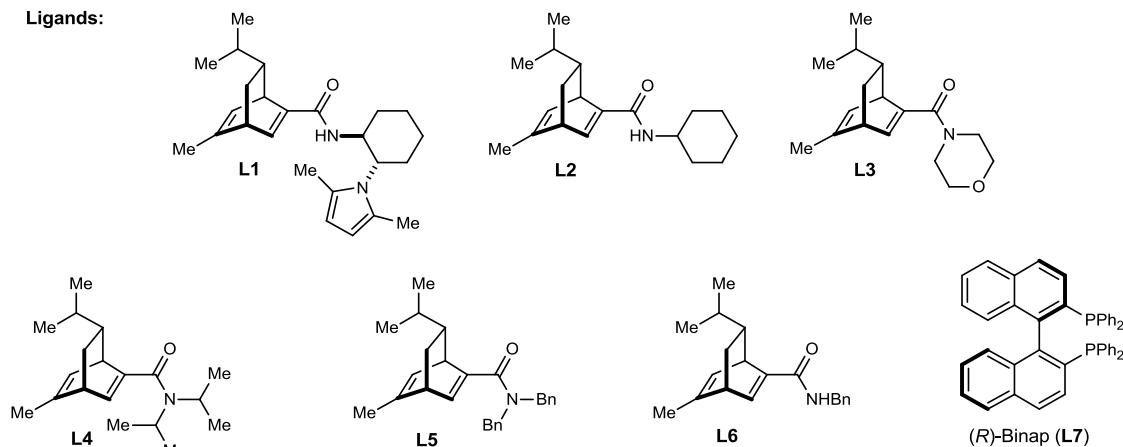
The alkenylarenes thus prepared were then subjected to RCAA conditions.

2.3. RCAA of Alkenylarenes

To maximise the chances of productive reactions taking place, alkenylarene **82a** containing the strongly electron-withdrawing nitro group at the *p*-position was selected as a test substrate (Table 1.1). As a preliminary gauge of reactivity, the addition of PhB(OH)_2 to **82a** was performed using $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol%) and KOH (2.5 equiv.) in dioxane/ H_2O at 80 °C under microwave (μw) irradiation for 30 min. This experiment resulted in 42% conversion into *rac*-**83a** (entry 1). Next, the use of chiral ligands was evaluated in combination with $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ as a precatalyst to assess whether **83a** could be obtained with improved conversions and in high enantioselectivity. Chiral diene ligands have been shown to provide excellent results in RCAA⁷⁶⁻⁹¹ and, in view of the success obtained with secondary amide-containing ligand **L1**⁹²⁻⁹³ in our group's previous study of the RCAA of alkenylheteroarenes⁴³, this diene was evaluated first.



Ligands:



Entry	Ligand	Conversion (%) ^b	ee (%) ^c
1	— ^d	42	n/a
2	L1	35	97
3 ^e	L1	70	95
4	L2	24	95
5	L3	76	70
6	L4	84	87
7	L5	>95 ^f	95
8	L6	44	90
9	L7	66	97

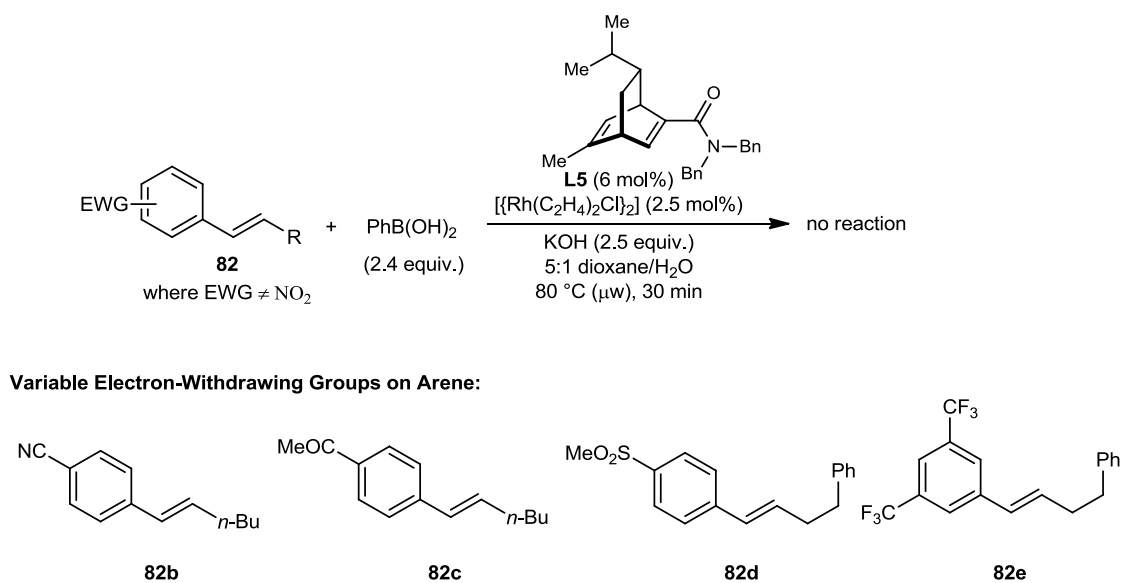
^a Reactions were conducted using 0.20 mmol of **82a** in dioxane (0.5 mL) and H_2O (0.1 mL). ^b Determined by ^1H NMR analysis of the unpurified reaction mixtures. ^c Determined by HPLC analysis on a chiral stationary phase. ^d $[\text{Rh}(\text{cod})\text{Cl}]_2$ was used in place of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, without an additional chiral ligand. ^e Reaction conducted at 120 °C for 30 min. ^f Product **83a** was isolated in 92% yield.

Table 1.1: Ligand Optimisation for the RCAA of **82a**

Although **L1** did lead to **83a** in 97% ee, the conversion was only 35% (entry 2). Increasing the temperature to 120 °C did increase the conversion with only a slight impact upon enantioselection (95% ee), but appreciable starting material remained (entry 3). Additional amide-containing chiral dienes were then investigated. The enantioselectivity remained high with ligand **L2** that lacks the pyrrole on the cyclohexyl ring, but the conversion was low (entry 4). Ligand **L3** containing a morpholine amide provided improved conversion (76%) at 80 °C, but the product was formed in only 70%

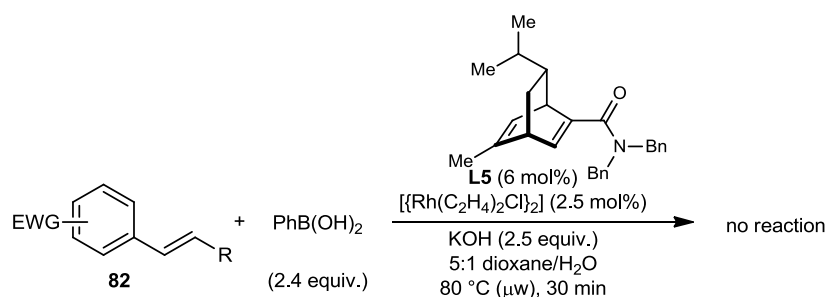
ee (entry 5). Ligands **L4** and **L5** containing tertiary amides gave further improved results (entries 6 and 7), with dibenzylamide-containing ligand **L5** giving the product in >95% conversion, 92% isolated yield, and 95% ee (entry 7). In contrast, ligand **L6** containing only one benzyl group on the amide nitrogen atom afforded inferior results (entry 8), further suggesting that under these conditions, a tertiary amide in the ligand is beneficial for high conversion. Finally, (*R*)-Binap (**L7**) was tested for comparison and although the enantioselectivity was high, the reaction did not go to completion (entry 9). On the basis of these results, ligand **L5** was selected for further study. Using ligand **L5**, other reaction parameters such as catalyst loading, solvent and reaction time were also optimised.

Having identified the optimum set of conditions, substrates containing an electron-withdrawing group other than a *p*-nitrophenyl group were tested (Scheme 1.38A). Unfortunately, attempts to arylate substrates **82b-82e** led to poor conversion to the desired product, which were too low to warrant further purification. Attempts to activate these substrates by changing reaction parameters proved to be unfruitful, leading either to recovery of starting material or the formation of various undesired products. These results highlight the strong electron-withdrawing influence of a nitro group and the ability of a *p*-nitrophenyl group to activate adjacent alkenes toward RCAA.

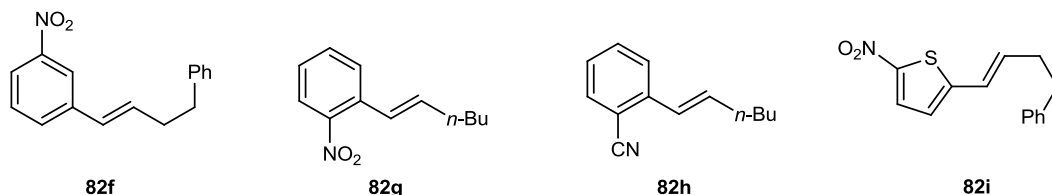


Scheme 1.38A: RCAA of Alkenylarenes

Next, substrates containing an electron-withdrawing group at various positions of the electron-deficient arene were subjected to our RCAA conditions (Scheme 1.38B). Not surprisingly, substrate **82f** did not participate in rhodium-catalysed arylation. In this case, the alkene is not conjugated to the nitro group of the adjacent *m*-nitrobenzene moiety. As a result, insufficient polarisation of the alkene renders it inactive toward RCAA.



Variable Position of Electron-Withdrawing Group on Arene:

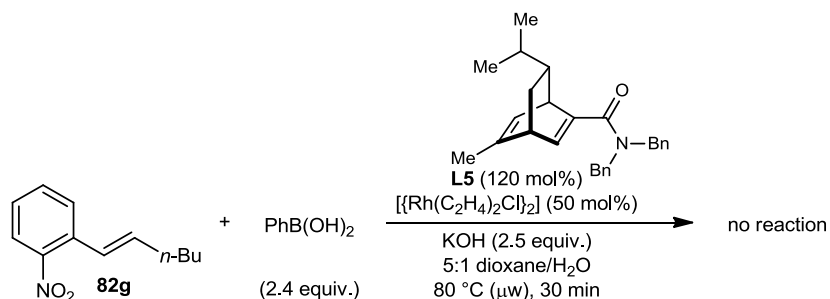


Scheme 1.38B: RCAA of Alkenylarenes

More intriguing was the failure of substrate **82g** to undergo conjugate arylation. We believed that the nitro group at the *o*-position of the arene in substrate **82g** would be conjugated to the adjacent alkene and impart a stronger electron-withdrawing influence in comparison to the *p*-nitrobenzene-containing substrate **82a**. Although the true reason for the inactivity displayed by substrates **82g** and **82h** toward RCAA remains unclear, it is possible that several factors may be inhibiting one or more key steps in the catalytic cycle for the rhodium-catalysed arylation of these particular *o*-substituted substrates. A likely explanation may be that due to the size and close proximity of the nitro and cyano group to the alkene in substrates **82g** and **82h** respectively, the p-orbitals on the alkene

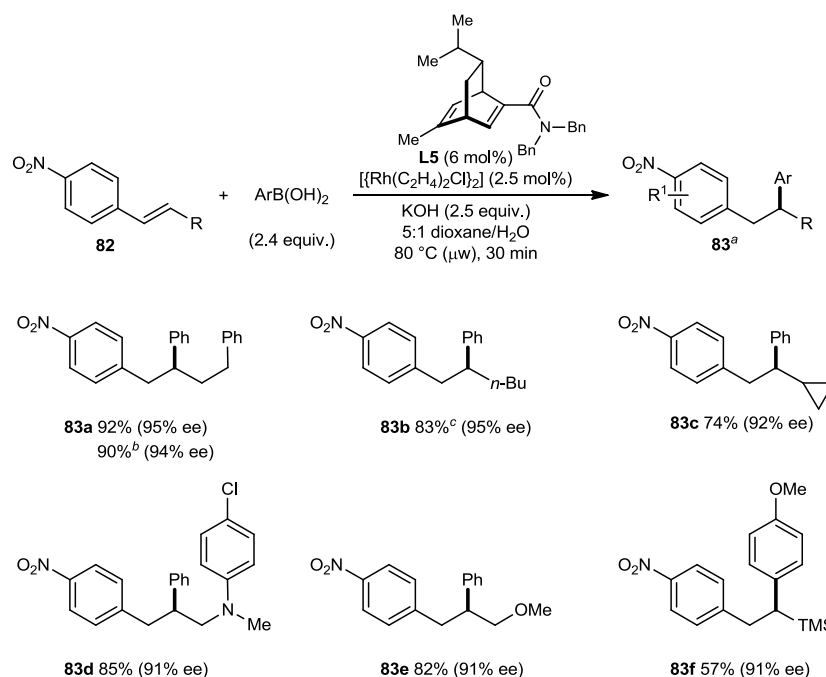
and the adjacent arene may twist out of plane, thus breaking the conjugation needed for RCAA.

We also considered the possibility that *o*-substituted substrates such as **82g** and **82h** may be poisoning the catalyst by binding to it too strongly and thus preventing it from re-entering the catalytic cycle. To test this theory, one reaction using **82g** was conducted using stoichiometric quantities of the rhodium precatalyst and the chiral diene ligand **L5** (Equation 1.7). As before, no arylated product was observed.



Equation 1.7: Catalyst-Poisoning Test in RCAA of Alkenylarenes

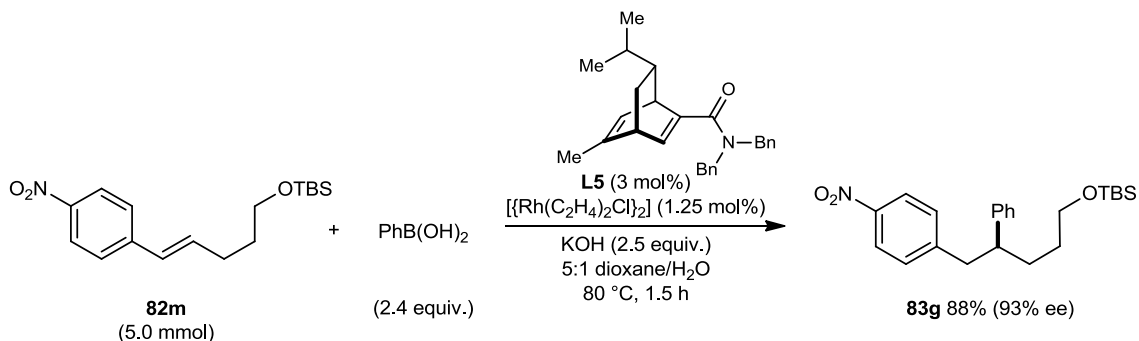
Equipped with the knowledge that placement of a nitro group at the *p*-position of the alkenylarene ring is crucial for success, the addition of arylboronic acids to various β -substituted alkenyl-*p*-nitroarenes was investigated (Scheme 1.38C). The range of tolerated substituents at the β -position of the alkene include simple linear alkyl groups (products **83a**, and **83b**), a cyclopropyl group (product **83c**), an allyl amine (product **83d**), an allyl ether (product **83e**) and a trimethylsilyl (product **83f**) substituent. The modest yield of product **83f** may be attributed to the steric hindrance provided by the bulkier trimethylsilyl group. Thermal heating was found to be as effective as microwave heating, as evidenced by a reaction conducted under otherwise identical conditions (product **83a**^b).



^a Unless otherwise stated, reactions were conducted using 0.20 mmol of **82**. Cited yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. ^b Reaction conducted under thermal heating under otherwise identical conditions. ^c Reaction performed using 1.0 mmol of **82j** at 80 °C under thermal heating for 1 h, using 1.25 mol% of Rh and 3 mol% of **L5**.

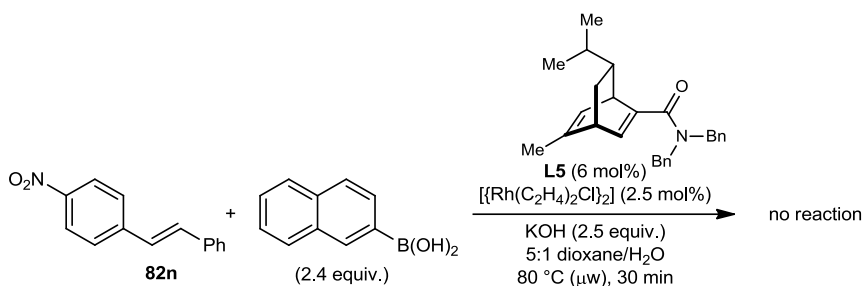
Scheme 1.38C: Scope of β -substituents in RCAA of Alkenyl-*p*-Nitroarenes

Furthermore, to test the practical applicability of this process, thermal heating was employed in the addition of phenylboronic acid to **82m** on a 5.0 mmol scale with 1.25 mol% of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ and 3 mol% of **L5** at 80 °C for 1.5 h, which provided **83g** in 88% yield and 93% ee, thus demonstrating the reaction to proceed smoothly on a preparative scale and at a reduced catalyst loading (Equation 1.8).



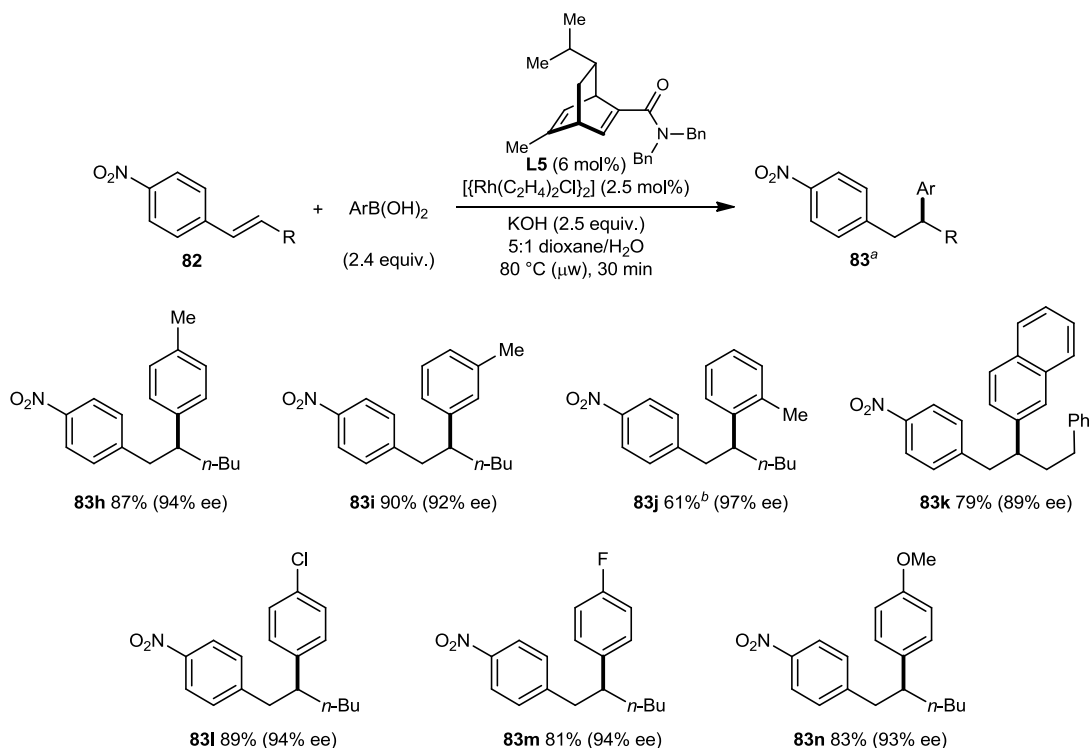
Equation 1.8: Preparative-Scale RCAA of 2-Alkenyl-*p*-Nitroarene

Substrate **82n** containing a β -aryl substituent did not undergo RCAA (Equation 1.9).



Equation 1.9: RCAA of β -Aryl Alkenyl-*p*-Nitroarene

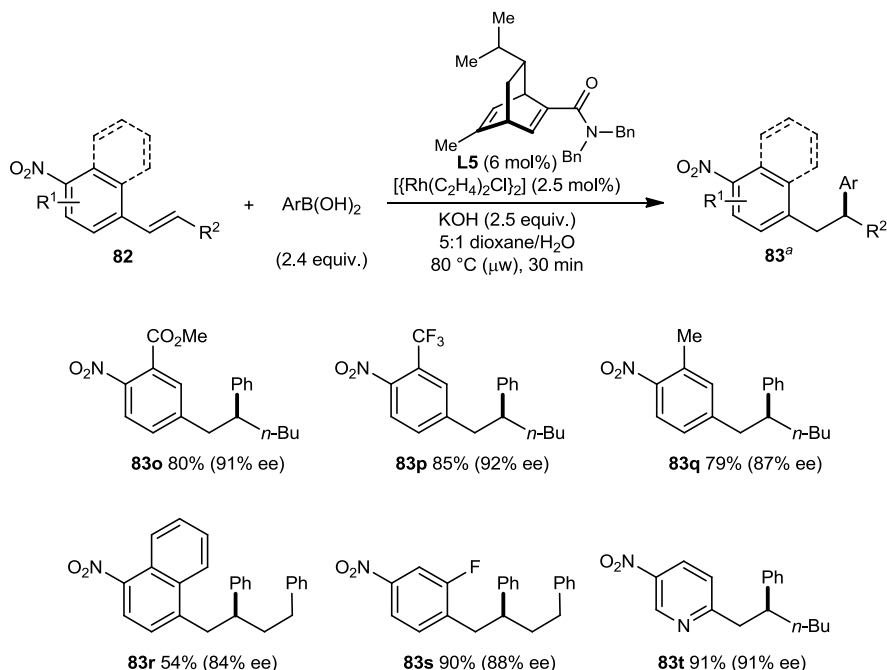
Regarding the scope of the nucleophile (Scheme 1.38D); *p*-, *m*- and *o*-tolyl boronic acid were competent reaction partners in this process (products **83h-83j**, respectively). The reaction of sterically demanding *o*-tolylboronic acid with substrate **82j** required a reaction time of 1 h to afford **83j**. Arylboronic acids containing electron-withdrawing or electron-donating substituents were also employed in our RCAA (products **83l-83n**).



^a Unless otherwise stated, reactions were conducted using 0.20 mmol of **82**. Cited yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. ^b Reaction time was 1 h.

Scheme 1.38D: Scope of Arylboronic Acids in RCAA of Alkenyl-*p*-Nitroarenes

In addition to a *p*-nitrophenyl group, the process is also tolerant of multisubstituted arenes (Scheme 1.38E). Other arenes that provide effective activation include *m*-carbomethoxy-*p*-nitrophenyl (product **83o**), *p*-nitro-*m*-(trifluoromethyl)phenyl (product **83p**), *m*-methyl-*p*-nitrophenyl (product **83q**), *p*-nitronaphthyl (product **83r**), *o*-fluoro-*p*-nitrophenyl (product **83s**), and a 5-nitro-2-pyridyl (product **83t**) ring.

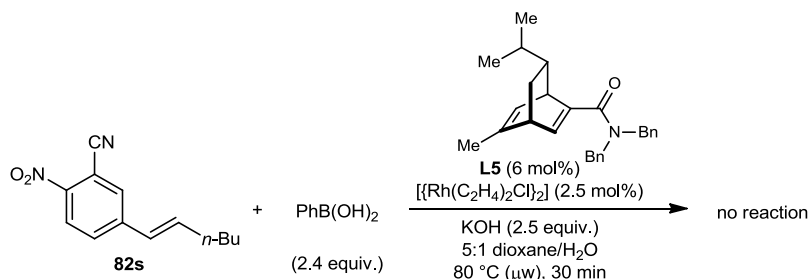


^a Unless otherwise stated, reactions were conducted using 0.20 mmol of **82**. Cited yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis.

Scheme 1.38E: Scope of Substitution on Arene in RCAA of Alkenyl-*p*-Nitroarenes

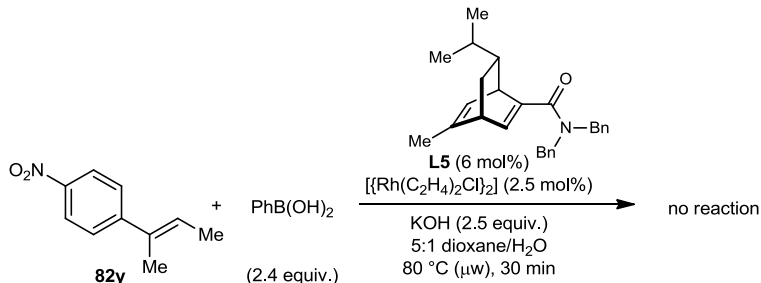
The powerful effect of a *p*-nitrophenyl group allowed us to address a problem discovered during our group's recent study of enantioselective rhodium-catalysed addition of arylboronic acids to alkenylheteroarenes, which identified a 2-pyridyl group as providing insufficient activation of an adjacent alkene for arylation to proceed efficiently.⁴³ Gratifyingly, 2-alkenylpyridine **82v** containing a 5-nitro group underwent arylation to give product **83t** in high yield and enantioselectivity (Scheme 1.38E).

Surprisingly, substrate **82s** containing a *m*-cyano-*p*-nitrophenyl group failed to arylate under our developed set of conditions (Equation 1.10). The reasons for this anomaly are unclear.



Equation 1.10: RCAA of Substrate Containing a *m*-Cyano-*p*-Nitrophenyl Group

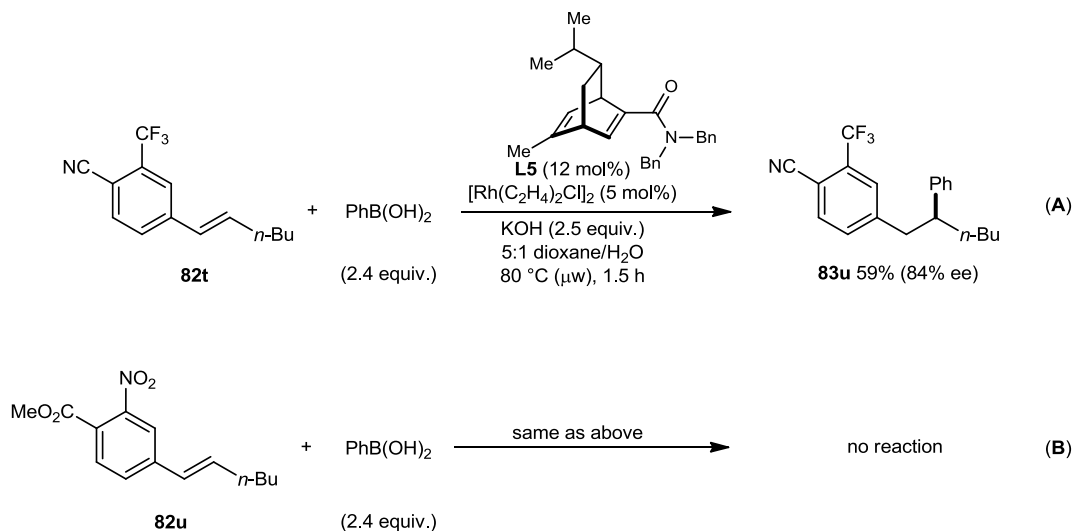
As noted previously, examples of RCAA of electron-deficient α,α -disubstituted alkenes are rare in literature. Nevertheless, arylation of an α,α -disubstituted alkenyl-*p*-nitroarene **82y** was attempted in our study (Equation 1.11). Disappointingly, none of the arylated product was observed.



Equation 1.11: RCAA of α,α -Disubstituted Alkenyl-*p*-Nitroarene

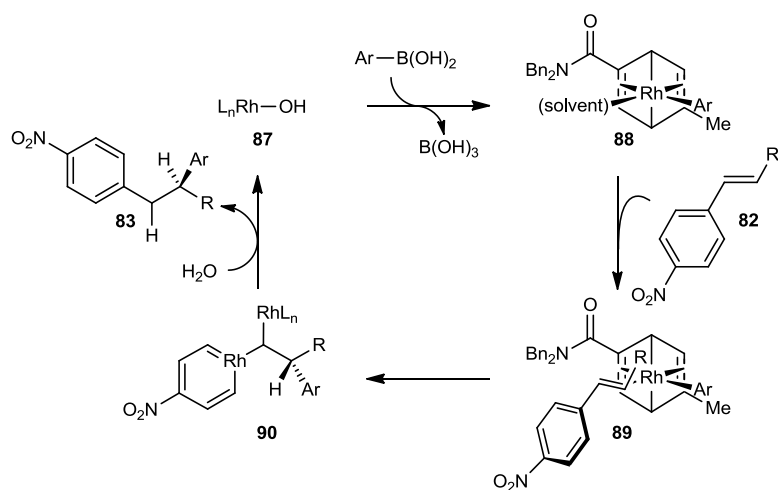
We have previously discussed our efforts to employ alkenylbenzene substrates containing a *p*-electron-withdrawing substituent other than a nitro group, which led to poor conversion into mixtures of identified undesired products (Scheme 1.38A). We rationalised that the placement of an electron-withdrawing group other than a nitro group at the *p*-position along with another electron-withdrawing substituent would help to further activate the adjacent alkene toward RCAA. Pleasingly, substrate **82t** containing a *p*-cyano-*m*-(trifluoromethyl)phenyl group did undergo arylation in 59%

yield and 84% ee in the presence of 10 mol% of the rhodium–chiral diene complex after 1.5 hours (Equation 1.12A). Substrate **82u** containing a *p*-carbomethoxy-*m*-nitrophenyl group was also subjected to similar RCAA conditions. Unfortunately, only trace amounts of the arylated product was observed (Equation 1.12B).



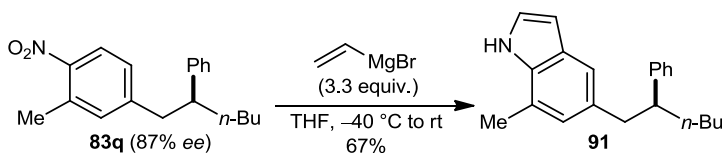
Equation 1.12: RCAA of *p*-Cyano-*m*-(trifluoromethyl)phenyl Group-Containing Alkenylarene

A possible mechanism for the RCAA of electron-deficient alkenyl-*p*-nitroarenes is illustrated in Scheme 1.39. Treatment of [Rh(C₂H₄)₂Cl]₂ and **L5** with KOH results in formation of chiral diene-ligated rhodium hydroxide **87**. Transmetalation of **87** with the arylboronic acid leads to the formation of rhodium–aryl species **88**, where the rhodium–aryl linkage is positioned *trans* to the more electron-deficient alkene. Coordination of the alkenylarene **82** to the remaining binding site of **88** then occurs as depicted in **89** to minimise unfavourable nonbonding interactions between the arene and the amide substituent of the ligand. Arylrhodation of the bound substrate results in the formation of intermediate **90**, which then undergoes hydrolysis to regenerate the rhodium hydroxide **87**, liberating the product **83**.



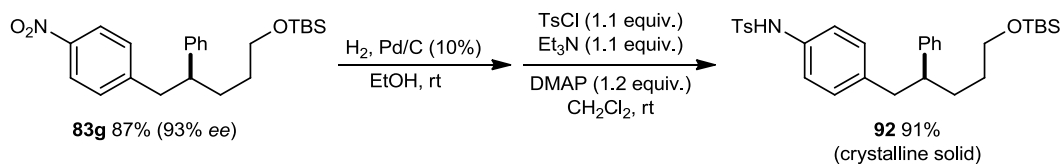
Scheme 1.39: Possible Mechanism for RCAA of Electron-Deficient Alkenyl-*p*-Nitroarenes

Nitroarenes are well-known to undergo a range of transformations, making them versatile intermediates in the preparation of dyes, pharmaceuticals and other functional compounds.⁹⁴ In order to demonstrate the synthetic utility of the arylation products described herein, **83q** was smoothly converted into indole **91** in 67% yield by treatment with vinylmagnesium bromide according to the method of Bartoli and co-workers (Equation 1.13).⁹⁵⁻⁹⁶



Equation 1.13: Indole Synthesis

Finally, in order to determine the absolute stereochemistry of the arylated products, the nitro group in **83g** was reduced to the corresponding amine and then tosylated to give **92** as a white crystalline solid (Scheme 1.40).



Scheme 1.40: Manipulation of Nitro Group

The absolute stereochemistry of compound **92** was then determined by single crystal X-ray crystallography and found to be in the (*S*)-configuration for the major enantiomer (Figure 1.3).

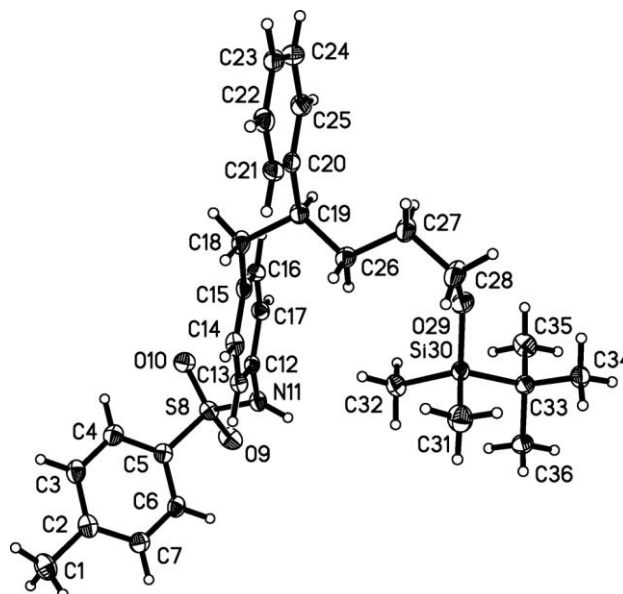
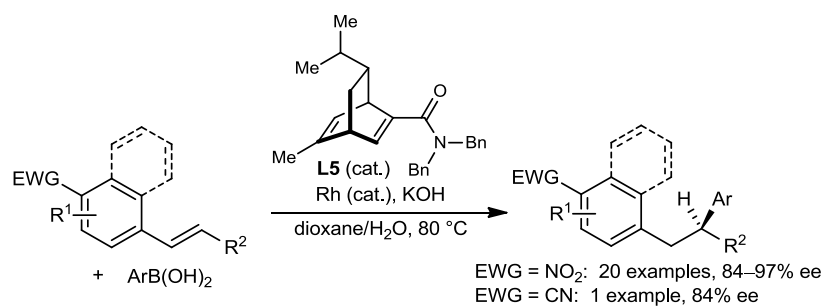


Figure 1.3: ORTEP Drawing of **92** with Ellipsoids Set at 50% Probability

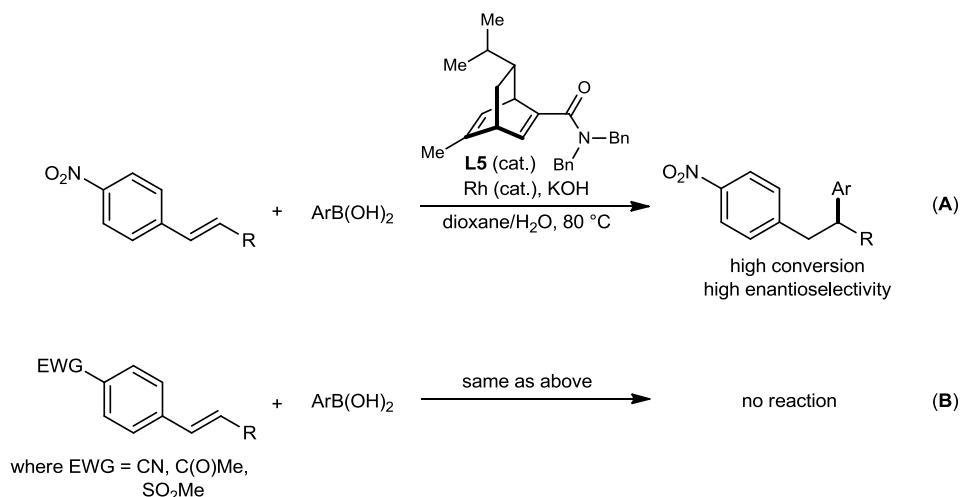
3. Conclusions

In summary, a new dibenzylamide-containing chiral diene ligand **L5** has been prepared, which enables highly enantioselective rhodium-catalysed additions of arylboronic acids to alkenyl-*p*-nitroarenes and an alkenyl-*p*-cyano-*m*-(trifluoromethyl)arene to take place under mild conditions (Scheme 1.41).⁹⁷ These reactions represent, to the best of our knowledge, the first examples of catalytic asymmetric addition of air- and moisture-stable organometallic reagents to alkenes activated by electron-deficient arenes.



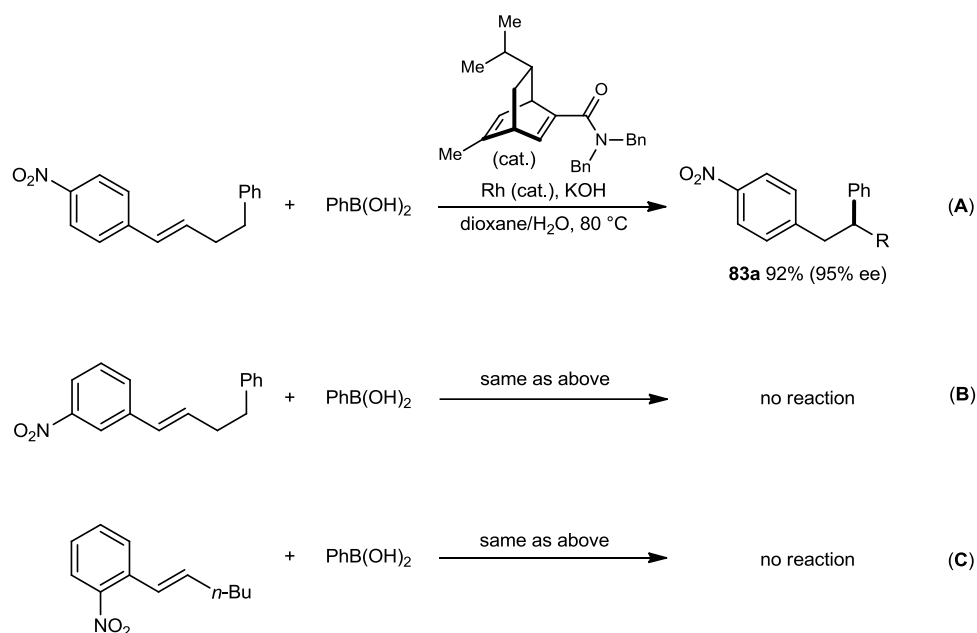
Scheme 1.41: RCAA of Electron-Deficient Alkenylarenes

The powerful electron-withdrawing influence of a nitro group was demonstrated by the placement of other electron-withdrawing groups on the arene (such as carbonyls, nitrile and sulfone groups), which failed to activate adjacent alkenes toward RCAA (Equation 1.14).



Equation 1.14: Electron-Withdrawing Influence of a Nitro Group in RCAA of Electron-Deficient Alkenylarenes

Work was also carried out to better understand the structural requisites necessary for this process. Alkenylarenes containing a *m*- or *o*-nitrobenzene moiety failed to participate in RCAA (Equation 1.15).

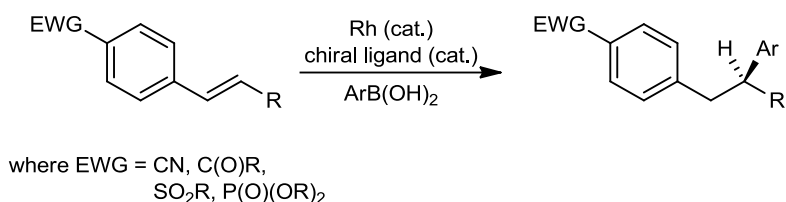


Equation 1.15: Structural Requirements for RCAA of Electron-Deficient Alkenyl-*p*-Nitroarenes

Extension of this concept to other classes of reactions may present exciting new opportunities for asymmetric catalysis. Studies in this area are currently underway in our group.

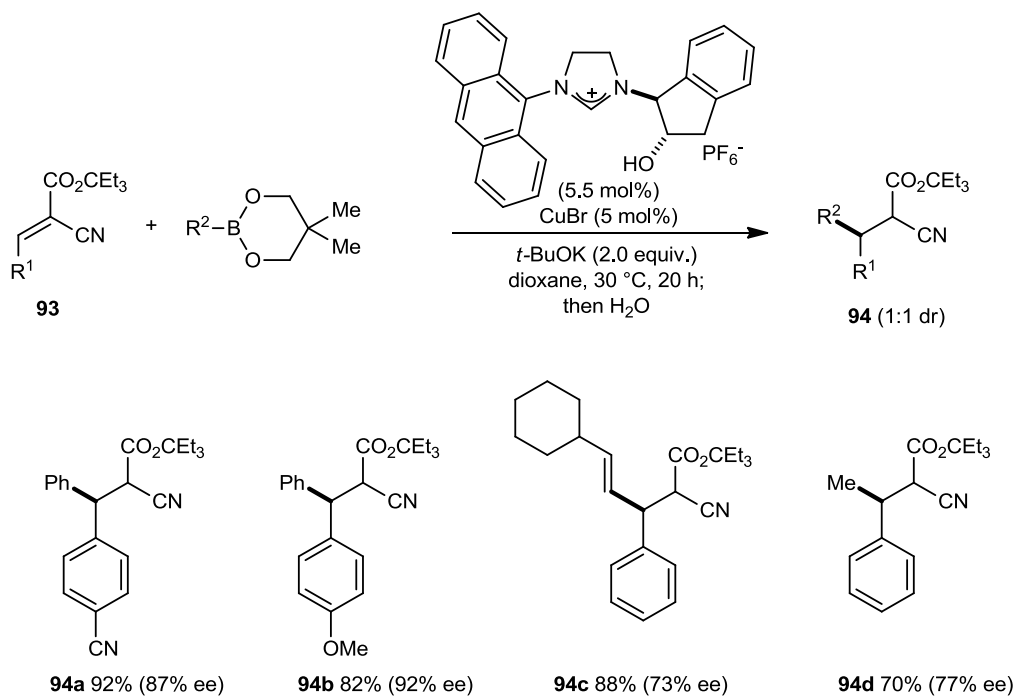
4. Future Work

As shown in Equation 1.14B, electron-withdrawing groups other than a nitro group, when placed at the *p*-position of an arene, failed to provide sufficient activation of the adjacent alkene toward RCAA. However, substrate **64t** containing a *p*-cyano-*m*-(trifluoromethyl)phenyl underwent arylation, albeit in low yield (Equation 1.12A). This result suggests that there is scope to increase the range of electron-deficient arenes that can be used as activating groups. Future developments in this area may rest upon the identification of more active catalysts and/or improved reaction conditions (Scheme 1.42).



Scheme 1.42: RCAA of Electron-Deficient Arenes not Containing a Nitro Group

Lastly, chiral NHCs are an emerging class of ligands in RCAA. In 2011, T. Hayashi and co-workers reported the 1,4-addition of various aryl, alkenyl, and alkyl organoborates to alkylidene cyanoacetates **93** catalysed by a NHC–copper complex (Scheme 1.43).⁹⁸ The ability to perform 1,4-additions by replacing rhodium with a less-expensive metal, such as copper, helps make this process significantly more valuable. The report also suggests that the development of novel NHCs might spur a new wave of conjugate addition chemistry catalysed by copper and other cheaper metals.



Scheme 1.43: Copper-Catalysed 1,4-Addition of Organoborates to Alkylidene Cyanoacetates

II. Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes with Ketones

1. Introduction

Nitrogen-containing aromatic heterocycles (azaarenes) are privileged structures that appear in numerous biologically active compounds such as natural products, pharmaceuticals, and agrochemicals (Figure 2.1). Therefore, the development of new methods for the incorporation of azaarenes into compounds, or to functionalise pre-existing azaarenes, are of high value.

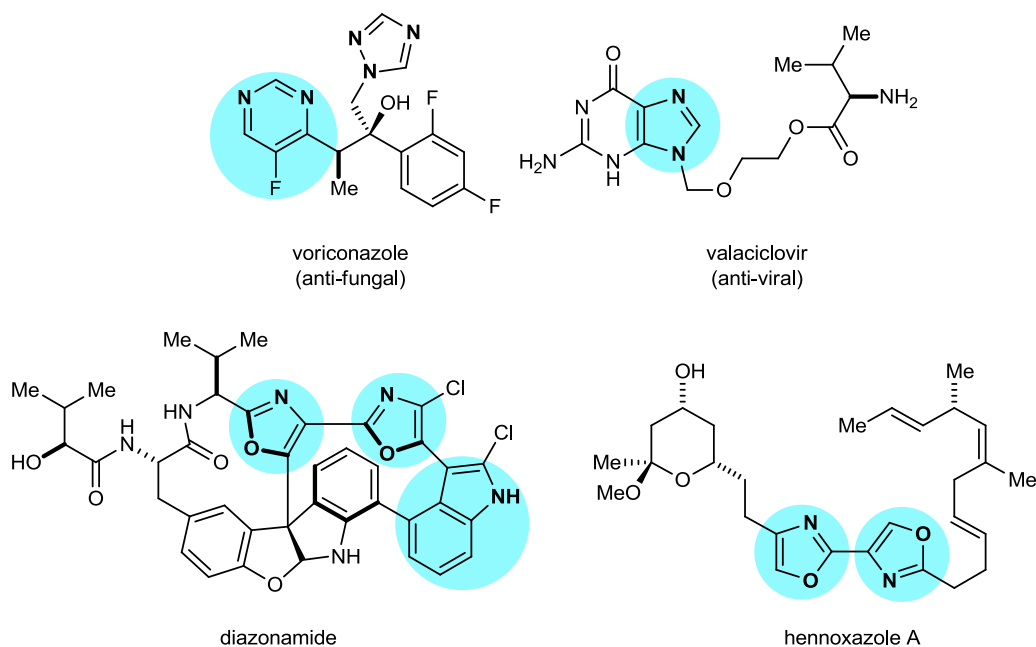
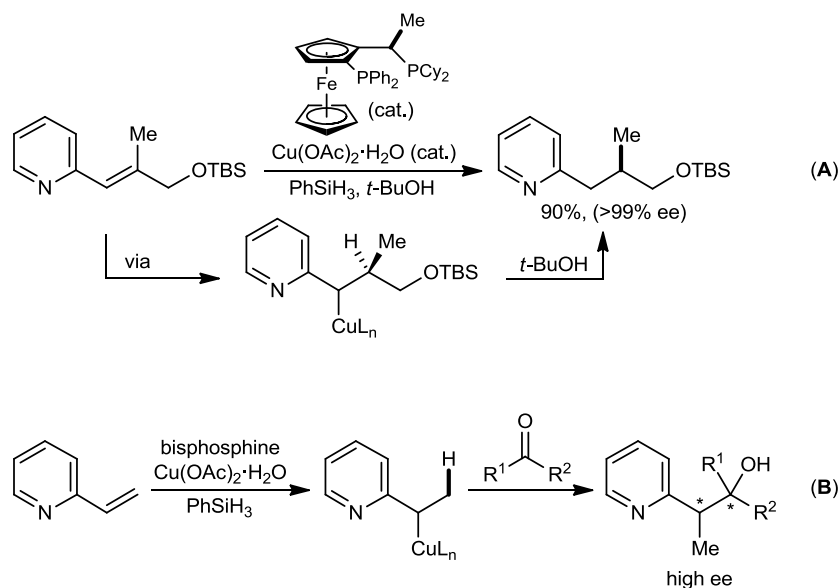


Figure 2.1: Aromatic Heterocycles in Natural Products and Therapeutic Agents

In this regard, recent efforts from our group have targeted the development of processes that exploit the ability of a suitably positioned C=N moiety within azaarenes to activate adjacent alkenes⁹⁹⁻¹⁰¹ toward catalytic enantioselective 1,4-additions.^{43, 102} The first of these reports described copper hydride-catalysed conjugate reduction¹⁰³⁻¹⁰⁶ of β,β -

disubstituted 2-alkenylazaarenes, which result in alkylazaarenes with a new stereogenic center at the β -carbon (Equation 2.1A).¹⁰²



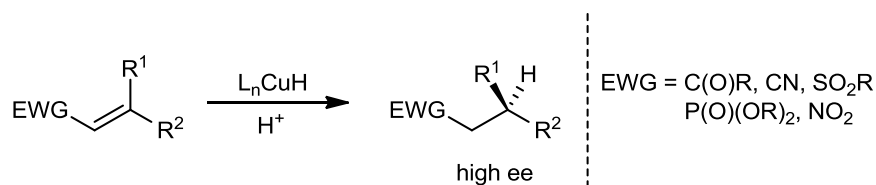
Equation 2.1: Catalytic Transformations of Alkenylazaarenes

Since these reactions likely proceed via the intermediacy of organocopper species that undergo protonation with $t\text{-BuOH}$, we questioned whether these intermediates could be trapped *in situ* with an alternative electrophile such as a ketone (Equation 2.1B), thereby delivering synthetically valuable alcohol-containing products with stereochemistry at both α - and β -carbons. Reports on copper hydride-catalysed conjugate reductions and its extension to tandem processes such as reductive aldol reactions are present in literature and are discussed in the following sections.

1.1. Copper Hydride (CuH)-Catalysed Conjugate Reductions

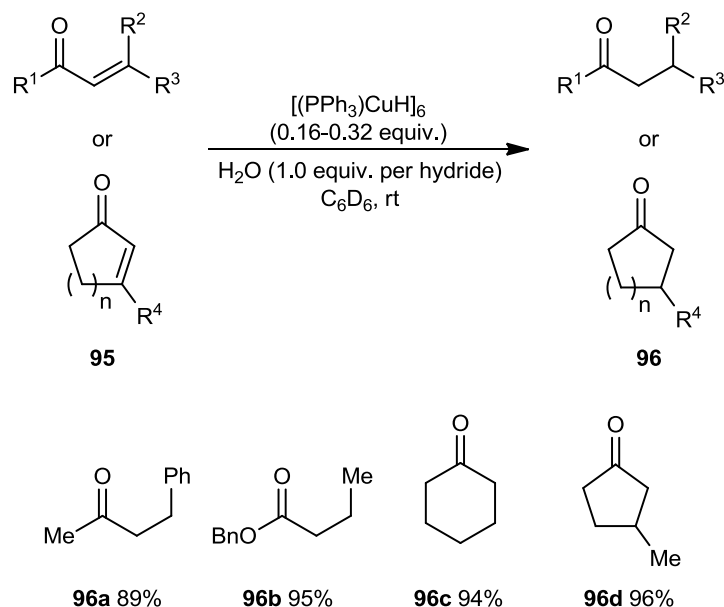
Conjugate reduction of α,β -unsaturated carbonyl compounds by organosilanes mediated by complexes of rhodium, platinum, palladium, and molybdenum are well-established.¹⁰⁷⁻

¹⁰⁹ However, the use of copper, a less-expensive metal, for the analogous transformation is a comparatively recent development (Equation 2.2).^{103, 106}



Equation 2.2: CuH-Catalysed Reduction of Alkenes Conjugated to Common Electron-Withdrawing Groups

Modern usage of CuH reagents is well-recognised to have begun with Stryker's reagent.¹¹⁰⁻¹¹⁴ In 1988, Stryker and co-workers reported the ability of this reagent, which exists as a phosphine-stabilised hexamer of the formula [(Ph₃P)CuH]₆, to effect conjugate reduction of carbonyl derivatives **95** (Scheme 2.1).

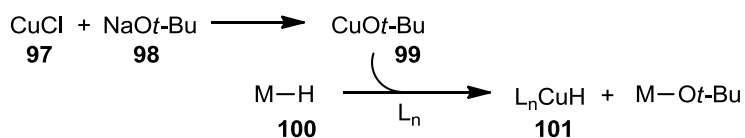


Scheme 2.1: 1,4-Reduction of Carbonyl Derivatives Catalysed by Stryker's Reagent

In this seminal report, highly regioselective 1,4-reduction, with near complete suppression of competing 1,2-reduction was observed. Mildness of reaction conditions and functional group compatibility adds to the merit of this process. For these reasons, Stryker's reagent was awarded the status of "Reagent of the Year" in 1991.

Interestingly, a subsequent report by Stryker identified molecular hydrogen as a possible source of hydride for the conjugate reduction of enones, thus allowing the use of sub-stoichiometric quantities of Stryker's reagent.¹¹⁵ However, a major drawback encountered in this report was the delivery of H₂ gas at very high pressures (>1000 psi), which in turn led to competing 1,2-reduction of enones to generate the corresponding alcohol. Hydrosilanes, which in general are inexpensive and environmentally friendly, have become the most frequent source of stoichiometric hydride (species **100**, Scheme 2.2) in modern CuH-catalysed reductions. Polymethylhydrosiloxane (PMHS), tetramethyldisiloxane (TMDS), Fleming's silane (PhMe₂SiH), triethoxysilane ((EtO)₃SiH) and phenylsilane (PhSiH₃) are examples of commonly used organosilanes.

An early protocol for the synthesis of ligated copper hydride reagents relied on the treatment of CuCl **97** with NaOt-Bu **98** producing CuOt-Bu **99**. Addition of a hydride source **100** (such as a hydrosilane) to pre-formed **99** in the presence of a ligand (PPh₃ in the case of Stryker's reagent) leads to the generation of the ligated CuH species **101** (Scheme 2.2). Since CuOt-Bu **99** is susceptible to oxidation, inert conditions are necessary for the *in situ* preparation of the CuH species **101**. This problem can be circumvented by the use of air-stable, easy-to-handle and commercially available Cu(OAc)₂·H₂O, which serves as a suitable substitute for CuOt-Bu. In the presence of a ligand and a hydrosilane reductant, Cu(OAc)₂·H₂O (where Cu has an oxidation state of +2) is efficiently reduced to the CuH species **101** (where Cu has an oxidation state of +1).



Scheme 2.2: Preparation of Ligated CuH Reagents

Switching from PPh₃ to chiral non-racemic ligands leads to the creation of a ligated CuH species capable of catalysing conjugate reductions in a diastereo- and enantioselective fashion. Although myriad CuH-catalysed asymmetric reductions have been reported to

date, virtually all have made use of a relatively small subset of either biaryl¹¹⁶⁻¹¹⁷ or ferrocenyl¹¹⁸ bisphosphine ligands, such as those illustrated in Figure 2.2.

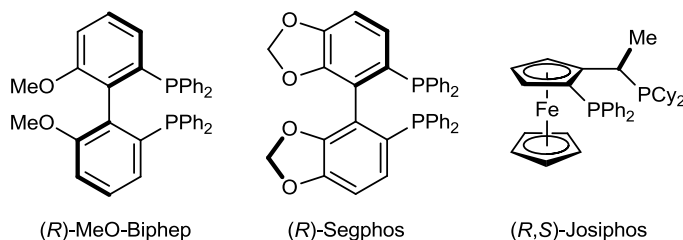
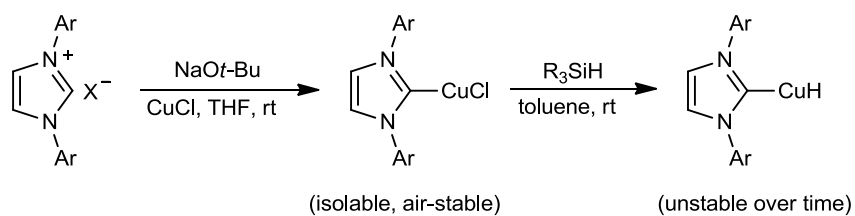


Figure 2.2: Examples of Bisphosphine Ligands Used in CuH-Catalysed Conjugate Reductions

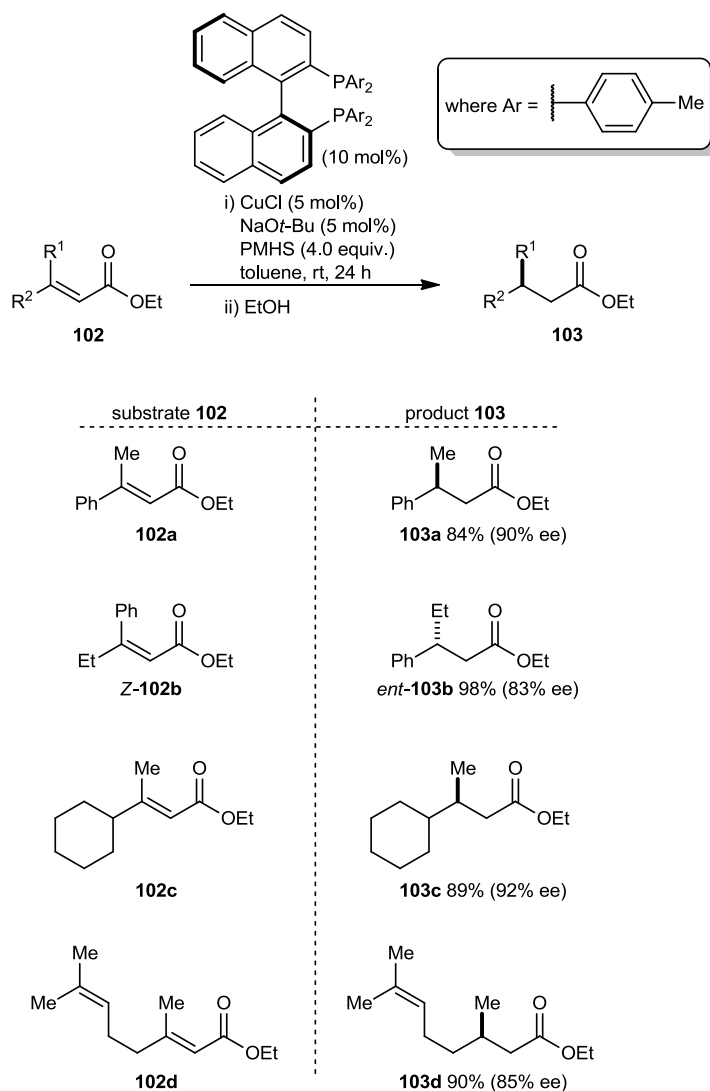
More recently, NHC ligands have presented yet another possibility for the generation of isolable and air-stable copper–carbene complexes (Scheme 2.3).¹¹⁹⁻¹²¹ Besides their stability in air, NHCs are electronically distinct ligands from their bisphosphine counterpart due to their strong σ -donating and weak π -accepting properties. They are structurally unique as well, possessing a likely linear array between the carbene carbon, copper and hydrogen atoms. However, chiral non-racemic carbene-based copper hydrides have not been applied in organic synthesis to date.



Scheme 2.3: Preparation of NHC–CuH Complex

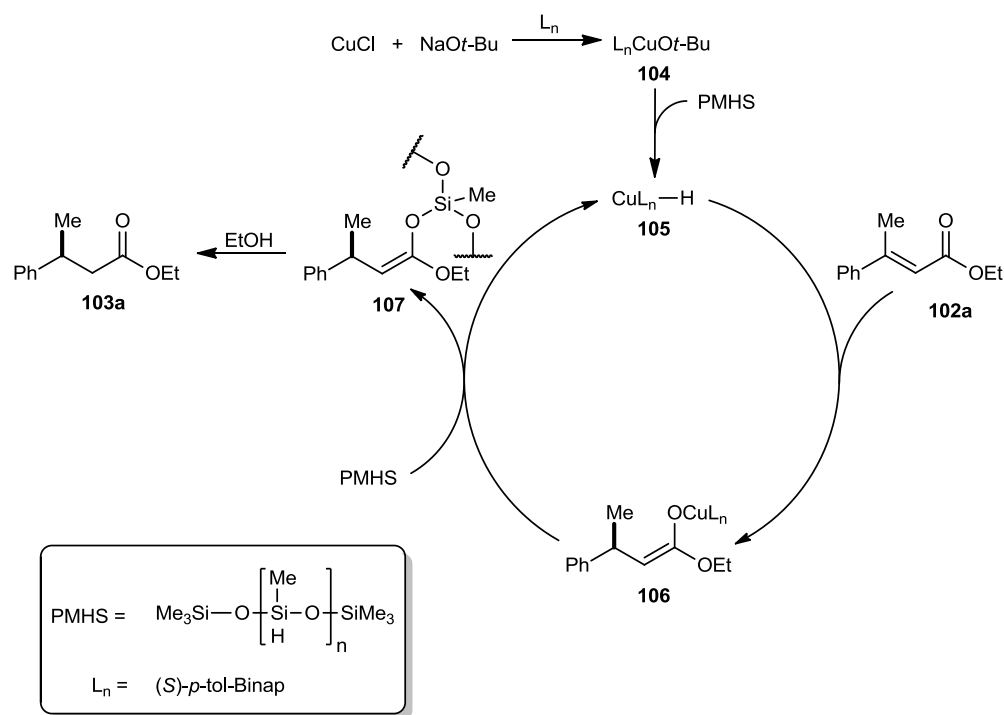
Enantioselective conjugate reductions catalysed by chiral phosphine-ligated CuH complexes and their application toward the synthesis of natural products and pharmaceutical drugs are well-documented.¹⁰³⁻¹⁰⁶ Detailed discussion of each report is beyond the scope of this thesis. Rather, only important breakthroughs and reports relevant to our study will be presented below.

One of the most significant breakthroughs was the first enantioselective conjugate reduction of α,β -unsaturated esters catalysed by the *in situ* formation of a chiral bisphosphine-ligated CuH species (Scheme 2.4).¹²²⁻¹²⁵ This report was published by Buchwald and co-workers in 1999.¹²² The reaction proceeded with high chemo- and enantioselectivity. *E*- and *Z*-isomers reacted to give opposite enantiomers (product **ent-103b**). Isolated alkenes were left intact, highlighting the tolerance of the reactive copper species toward other sensitive functional groups (product **103d**).



Scheme 2.4: Enantioselective CuH-Catalysed Conjugate Reduction of Enoates

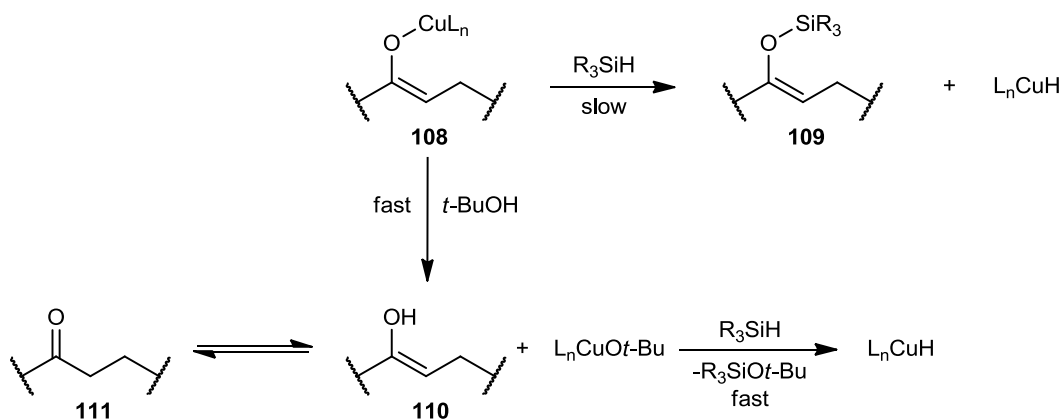
The mechanism for the conjugate reduction of enoate **102a** as proposed by Buchwald is illustrated in Scheme 2.5. Upon combining (*S*)-*p*-tol-Binap, CuCl and NaOt-Bu, formation of (*p*-tol-Binap)CuOt-Bu **104** most likely occurs. Addition of PMHS then results in a σ -bond metathesis between (*p*-tol-Binap)CuOt-Bu **104** and PMHS to generate (*p*-tol-Binap)CuH **105**. Asymmetric conjugate reduction of enoate **102a** then occurs, resulting in formation of a copper enolate intermediate **106** that subsequently undergoes σ -bond metathesis with PMHS to make a silylketene acetal **107** and regenerate the copper hydride **105**. The isolable product **107** when quenched with a proton source, such as EtOH, affords the enantioenriched ester **103a**.



Scheme 2.5: Catalytic Cycle of CuH-Catalysed Conjugate Reduction of Enoates

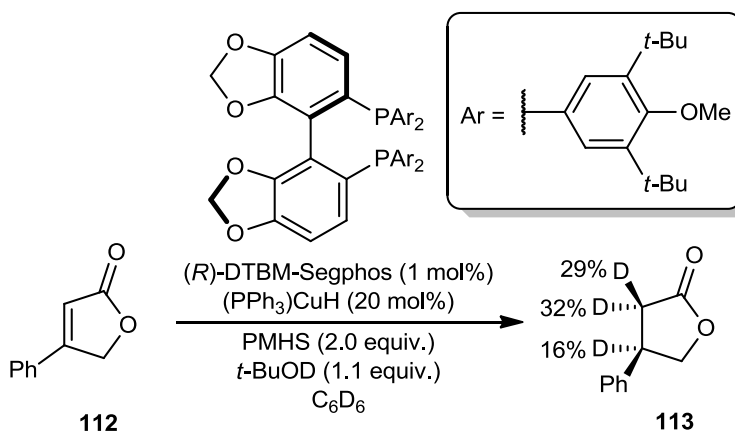
In Buchwald's report, EtOH was added in order to quench the reaction after ensuring complete consumption of the starting enoate. Advances in CuH chemistry since then have taken advantage of the tolerance of CuH complexes to alcohols and water. In fact, several methods rely on the presence of alcohols to enhance reaction rates. The role of this additive is usually ascribed to the more rapid quenching of the intermediate copper

enolate **108** generating a copper alkoxide, which is an ideal precursor to rapid reformation of copper hydride in the presence of excess silane (Scheme 2.6).



Scheme 2.6: Role of Alcohol in CuH-Catalysed Conjugate Reductions

Thus, the rate increase is presumably due to bypassing a slow metathesis step between Cu–O and Si–H bonds that is otherwise essential for regenerating CuH in the catalytic cycle. This proposed mechanism was supported in studies using *t*-BuOD (Equation 2.3).¹²⁶

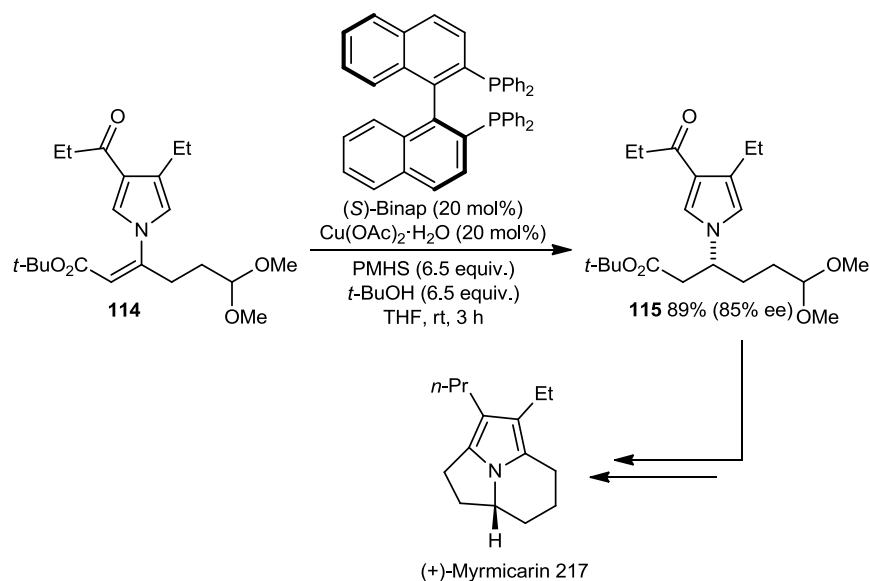


Equation 2.3: Deuteration Experiment: Effect of Alcohol in CuH-Catalysed Reductions

Asymmetric hydrosilylation of unsaturated lactone **112** revealed that most of the deuterium was incorporated at the α -position, while only small amounts were found at the

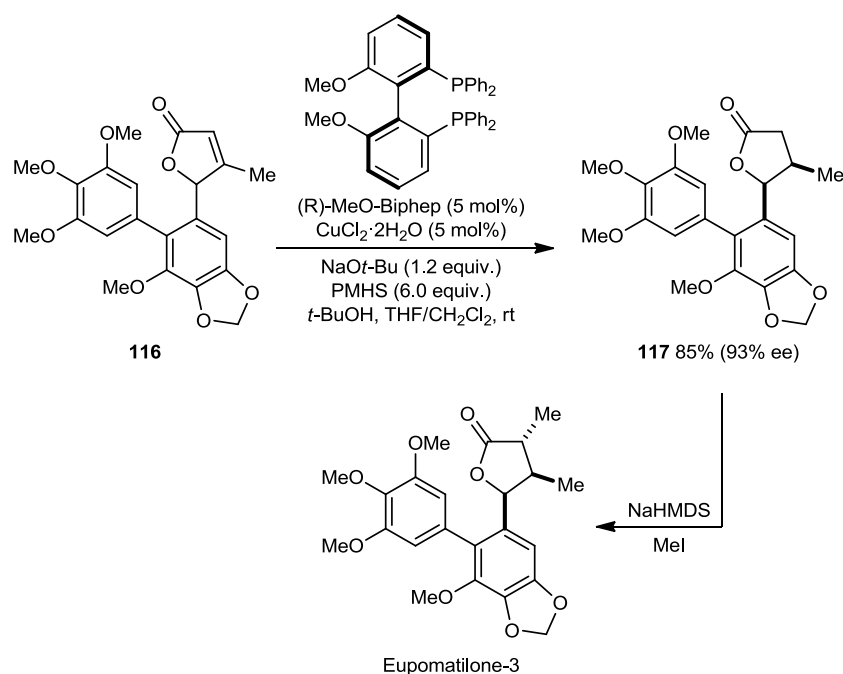
β -position. Thus, since no exchange occurs between PMHS and *t*-BuOD, it would seem that the rate enhancement may well be due to more rapid quenching of the copper enolate by the alcohol than by the silane. It is likely that the ligated CuH species and *t*-BuOD undergo a facile H/D-exchange at room temperature, which may account for the 16% deuterium incorporation observed at the β -site.¹²⁶

Since the discovery of enoates as suitable candidates for enantioselective CuH-catalysed conjugate reductions, other common functional groups such as carbonyls,¹²²⁻¹³³ nitriles,¹³⁴⁻¹³⁷ sulfones,¹³⁸⁻¹³⁹ phosphonates¹⁴⁰ and nitro groups¹⁴¹⁻¹⁴² have been shown to successfully activate adjacent alkenes toward similar asymmetric reductions. The utility of this process has also been demonstrated by its application in the synthesis of various natural products and therapeutic drugs. For example, enantioselective CuH-catalysed reduction of compound **114** formed a key step in the synthesis of the tricyclic myrmicarins alkaloid, myrmicarins-217 (Scheme 2.7).¹³² The myrmicarins are a family of alkaloids isolated from the poison gland secretions of the African ant species *Myrmecaria opaciventris*.¹⁴³



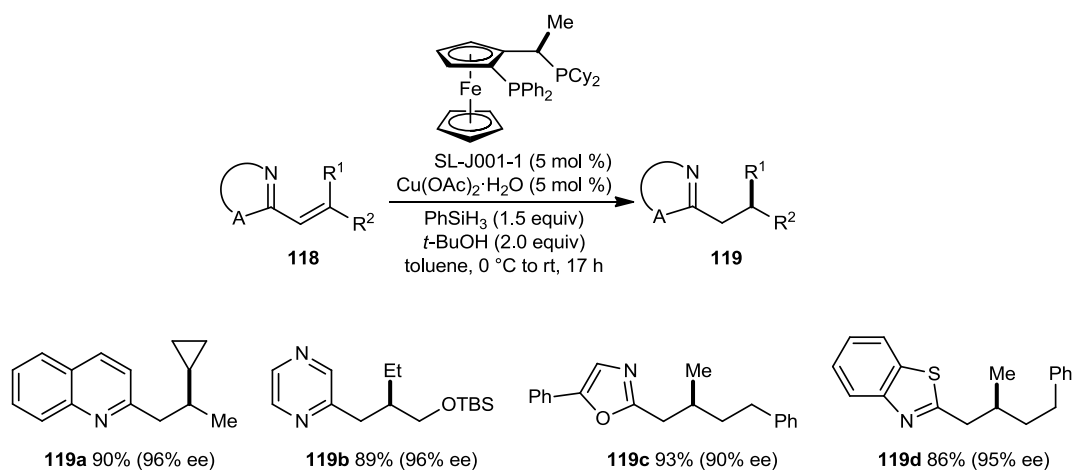
Scheme 2.7: Synthesis of Myrmicarins-217 by CuH-Catalysed Asymmetric 1,4-Reduction

CuH chemistry has also been applied toward the short asymmetric synthesis of the lignan eupomatilone-3 (Scheme 2.8).¹³³ Remarkably, in the presence of excess NaOt-Bu as base, an efficient kinetic resolution of racemic enone **116** occurred to afford the less reactive enantiomer with high diastereo- and enantioselectivity.^{124, 128} Eupomatilones are a family of lignans that were first isolated in 1991 from the Australian shrub *Eupomatia bennettii*.¹⁴⁴



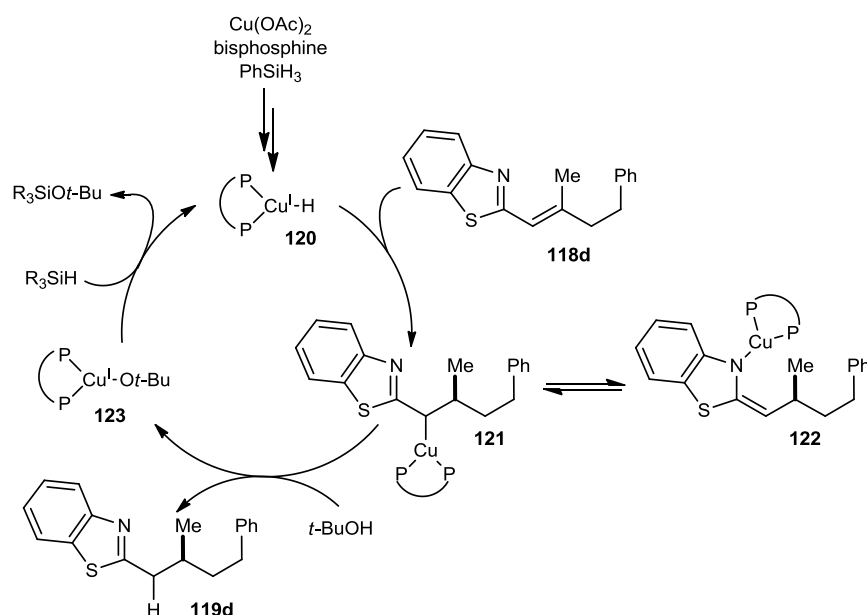
Scheme 2.8: Synthesis of Eupomatilone-3 by CuH-Catalysed Asymmetric 1,4-Reduction

Our group recently showed that azaarenes containing a suitably positioned C=N moiety could activate adjacent alkenes toward highly enantioselective CuH-catalysed conjugate reduction (Scheme 2.9).¹⁰² Given that heteroarenes such as oxazoles, thiazoles, pyridines, pyrazines, and others are ubiquitous in biologically active natural products, pharmaceuticals and agrochemicals, the ability to functionalise these privileged structures through asymmetric conjugate reduction should open up broad-ranging applications.



Scheme 2.9: CuH-Catalysed Asymmetric 1,4-Reduction of β,β -Disubstituted Alkenylazaarenes

The proposed mechanism is illustrated in Scheme 2.10, which we believe follows a relatively similar pathway as the accepted mechanism for CuH-catalysed 1,4-reductions.



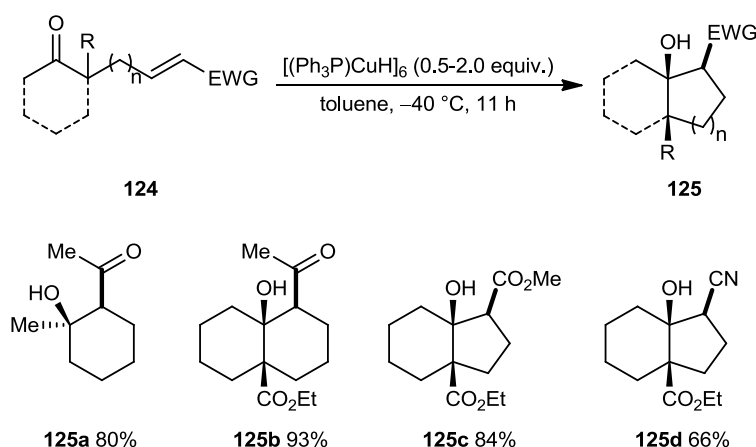
Scheme 2.10: Proposed Catalytic Cycle of CuH-Catalysed 1,4-Reduction of β,β -Disubstituted Alkenylazaarenes

Having proven that azaarenes could activate adjacent alkenes toward conjugate reductions, extension of this concept for tandem processes was sought. We questioned if the organocopper species **121** formed in the catalytic cycle could be trapped by an

electrophile other than a proton. Conjugate reduction-alkylation, conjugate reduction-cyclisation and conjugate reduction-allylic substitution reactions were some of the avenues considered. Efforts eventually focused on the conjugate reduction-aldol reaction of alkenylazaarenes with various carbonyl derivatives. A discussion of existing reports on CuH-catalysed reductive aldol couplings is presented below.

1.2. CuH-Catalysed Reductive Couplings

Prior to the discovery of copper as an effective metal for catalysing reductive aldol reactions, early reports made use of expensive transition metals such as rhodium, palladium, iridium or cobalt.¹⁴⁵⁻¹⁵⁵ In 2001, Chiu and co-workers demonstrated the use of copper as a suitable metal for similar reductive aldol reactions.¹⁵⁶⁻¹⁵⁷ Not surprisingly, these seminal reports made use of stoichiometric quantities of Stryker's reagent as the achiral reductant (Scheme 2.11).¹⁵⁷

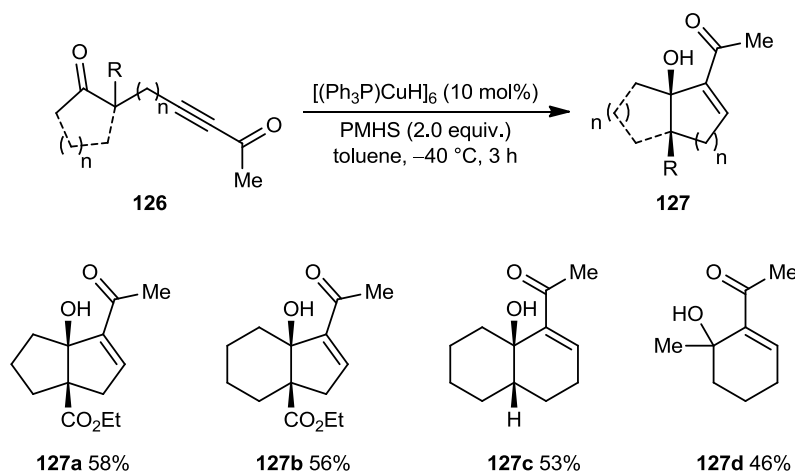


Scheme 2.11: Diastereoselective Cu-Mediated Aldol Cycloreduction Using Stryker's Reagent

At $-40\text{ }^{\circ}\text{C}$, the formation of a new 5- or 6-membered carbocycle proceeded with high diastereoselectivity leading to the generation of products bearing all-*cis* stereochemistry (products **125a-125d**). However, at an elevated temperature of $25\text{ }^{\circ}\text{C}$, the ester and the hydroxyl groups at the junction of the fused rings were found to be oriented *trans* to each other. These observations were attributed to the formation of the kinetically derived all-*cis* product at low temperature, while at higher temperatures the copper aldolate

intermediate could undergo a retro-aldol reaction to give the thermodynamically more stable *trans*-oriented product. Interestingly, alkenes conjugated to electron-withdrawing groups other than a ketone also underwent copper-catalysed aldol cycloreductions (products **125c** and **125d**). The report also noted that while *E*- and *Z*-olefinic substrates delivered products with the same stereochemical outcome, the *trans* isomer reacted at a faster rate than its *cis* isomeric counterpart.

In 2004, the same group also reported the reductive aldol cyclisation of alkynediones using sub-stoichiometric quantities of Stryker's reagent and PMHS as the source of hydride (Scheme 2.12).¹⁵⁸ Although these reactions may be viewed as a simple extension of Chiu's previous report (Scheme 2.11), the ability to perform the reactions using sub-stoichiometric quantities of Stryker's reagent adds to the merit of this methodology.

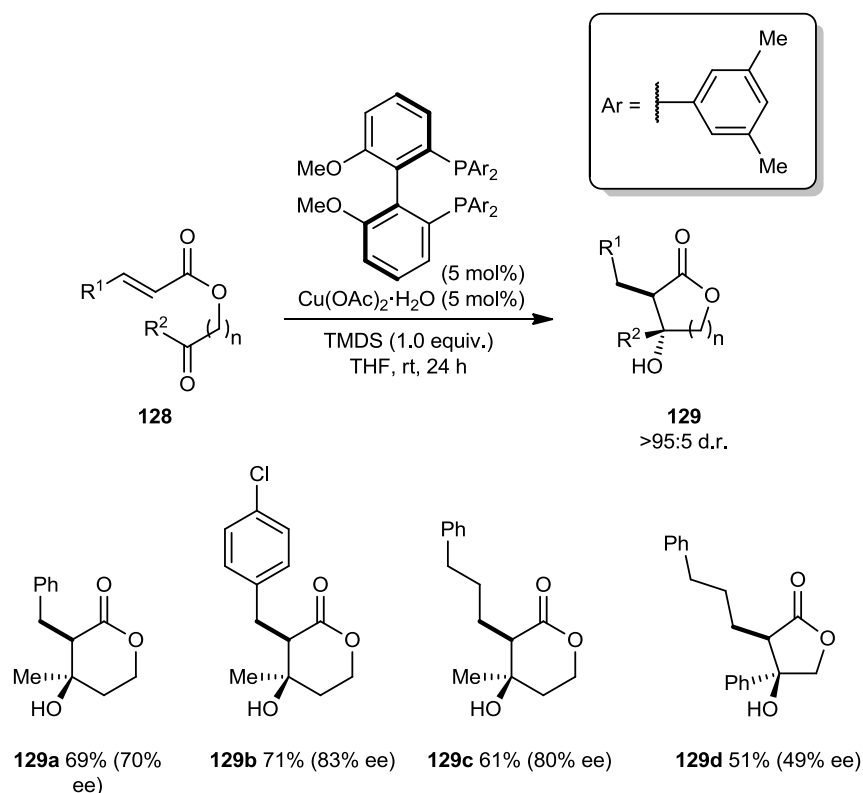


Scheme 2.12: Diastereoselective Cu-Catalysed Aldol Cycloreduction of Alkynediones Using Stryker's Reagent

The reductive aldol cyclisation of alkynediones provided β -hydroxycycloalkenones (products **127a-127d**), which are complementary to those obtained from intramolecular Baylis-Hillman reactions. Whereas β -substituted enones and ketones make poor Michael acceptors and electrophiles respectively for the Baylis-Hillman reaction, the reductive aldol cyclisations of the related alkynones **126** mediated by Stryker's reagent occurred at low temperatures and under mild conditions.

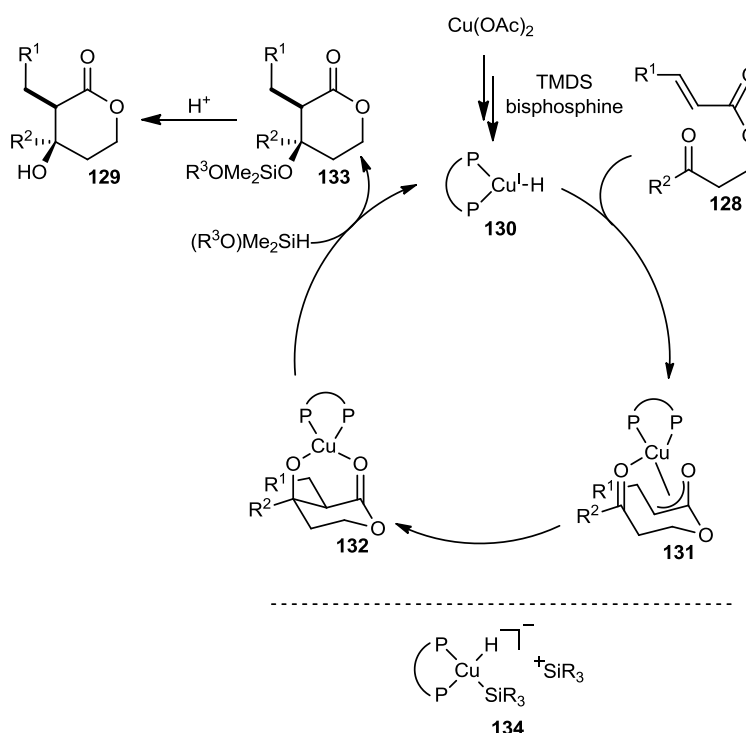
The copper-catalysed reductive aldol reactions reported by Chiu employed Stryker's reagent, which is achiral. Therefore, while the system may afford products with high levels of diastereoselectivity, generation of enantioenriched products was not possible. Enantioselective variants have been developed by making use of sub-stoichiometric quantities of metals such as rhodium, iridium and cobalt; however, the use of copper in transition metal-catalysed asymmetric reductive aldol reactions has only recently appeared in literature.

In 2005, our group described the first enantioselective copper-catalysed aldol cycloreductions (Scheme 2.13).¹⁵⁹ The β -Hydroxylactones **129a-129d** were formed in excellent diastereoselectivity (>95:5 in all cases). However, the enantioselectivities observed were modest.



Scheme 2.13: Diastereo- and Enantioselective Cu-Catalysed Aldol Cycloreduction for the Synthesis of β -Hydroxylactones

The report also noted the production of small quantities of uncyclised side products that had undergone reduction at the enoate and in some cases at the ketone. This observation indicates that the rate of σ -bond metathesis of the intermediate copper enolate with the siloxane is competitive with the rate of aldol cyclisation. A plausible catalytic cycle for the process was also presented (Scheme 2.14).

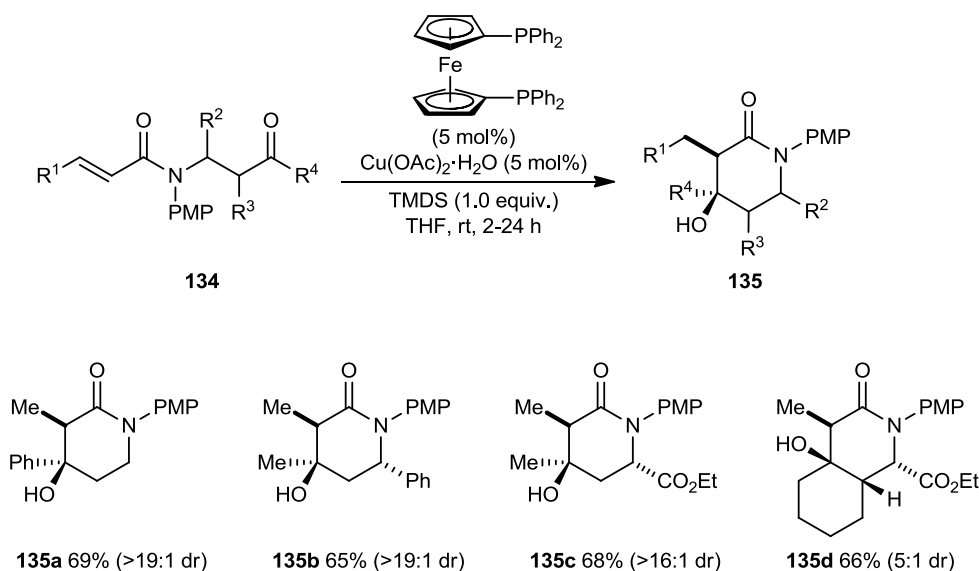


Scheme 2.14: Catalytic Cycle of Cu-Catalysed Aldol Cycloreductions

Presumably, in the presence of a bisphosphine ligand and TMDS, reduction of copper(II) occurs to generate a bisphosphine ligated copper(I)–hydride complex **130**, which then engages in hydrometalation with substrate **128** to generate the copper enolate **131**. Carbonyl addition results in the copper aldolate **132**, which then undergoes σ -bond metathesis with the siloxane to liberate the silylated product **133** (which is deprotected upon work-up to give product **129**), regenerating the copper(I) complex **130**. The report also suggests that alternative mechanisms that invoke the participation of copper species such as silyl hydrido cuprates **134** may also be operative. Furthermore, the role played by

the acetate counterion is unclear. The observed stereochemistry of the products presumably arises from preferential formation of the *Z*-copper enolate, coupled with chelation in the carbonyl addition step (as in **131**).

Later that year, our group reported related copper(I)-catalysed reductive aldol cyclisations for the generation of 4-hydroxypiperidin-2-ones **135** (Scheme 2.15).¹⁶⁰ In this report, *N*-alkyl-*N*-arylamides bearing no stereocenters, such as substrate **134a** (where R^2 and $R^3 = H$), smoothly underwent copper-catalysed reductive aldol cyclisation. Enantioenriched substrates **134b-134d** containing pre-existing stereocenters also cyclised to give the corresponding piperidinones **135b-135d**, respectively.



Scheme 2.15: Diastereoselective Cu-Catalysed Aldol Cycloreduction for the Synthesis of 4-Hydroxypiperidin-2-ones

The moderate to excellent levels of 1,2- and 1,3-asymmetric induction in these reactions may be rationalised by invoking the chelated chair-like conformations **136-138** shown in Figure 2.3, with substituents in the tether linking the amide enolate and the ketone preferring to adopt pseudoequatorial positions.¹⁶¹

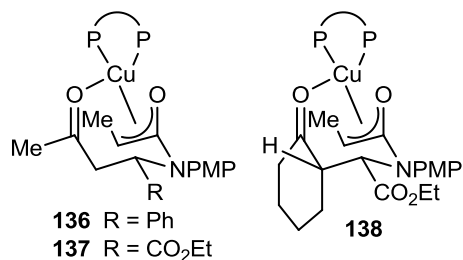
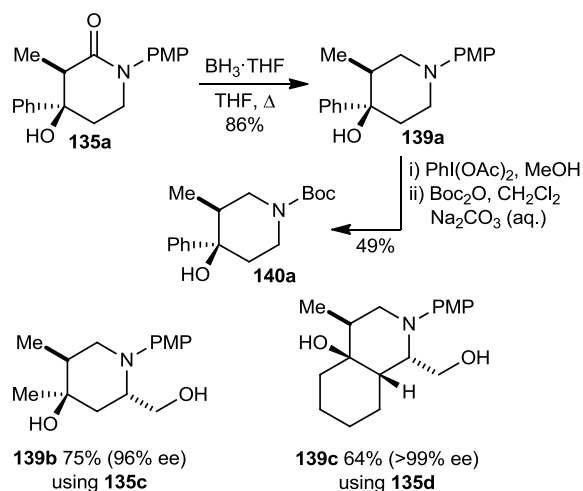


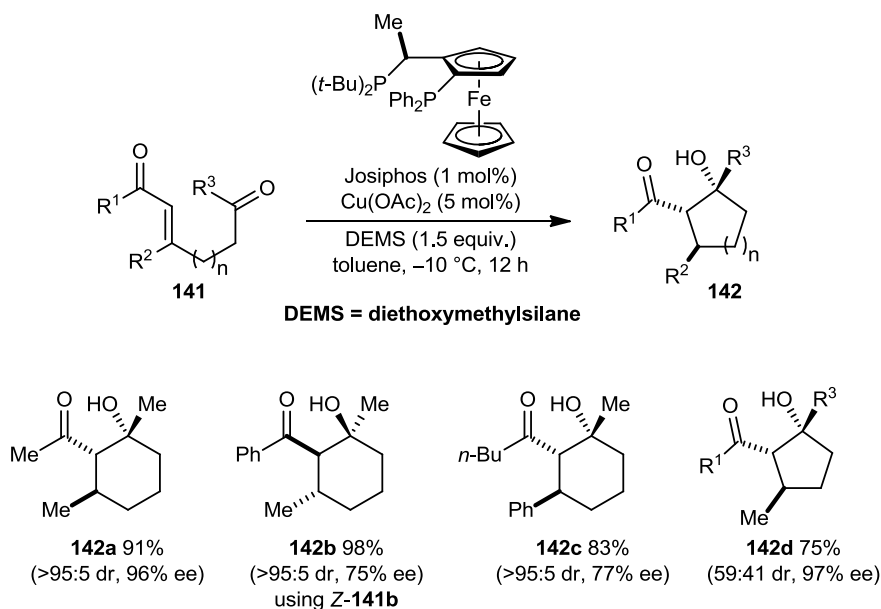
Figure 2.3: Possible Reactive Conformations for the Cyclisation of Substrates **134b-134d**

The synthetic utility of the piperidinone products was illustrated by a number of transformations (Scheme 2.16). Reductive removal of the carbonyl group by treatment of **135** with borane at reflux allowed entry to the piperidine ring system **139**, which is a ubiquitous structural feature of many natural products and biologically important compounds.¹⁶²⁻¹⁶³ **139a** was then converted into **140a** by oxidative removal of the *p*-methoxyphenyl (PMP) group followed by *in situ* treatment of the resulting amine with Boc₂O. The amide reduction of piperidin-2-ones **135c** and **135d** with borane was accompanied by reduction of the ethyl esters to give piperidines **139b** and **139c**, respectively. Polyhydroxylated piperidines are of considerable biological interest due to their potential to act as glycosidase inhibitors.¹⁶⁴



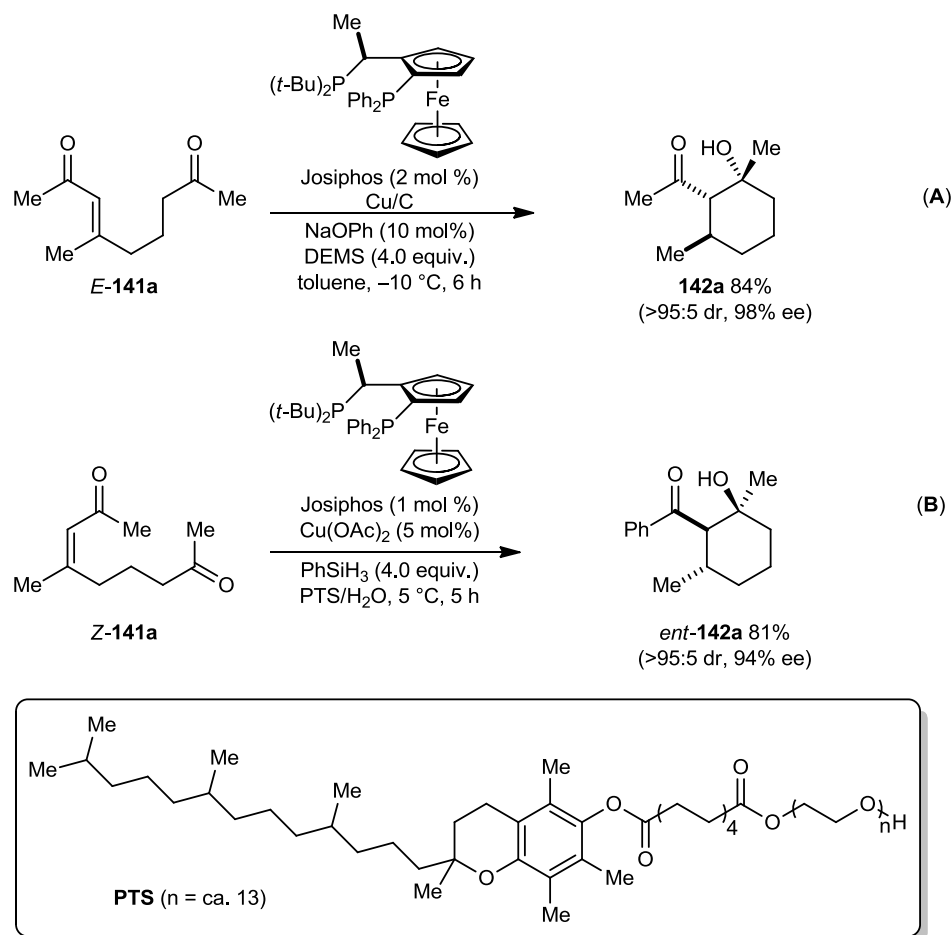
Scheme 2.16: Conversion of Piperidinone Products into Piperidines

In 2008, Lipshutz and co-workers reported highly enantioselective CuH-catalysed reductive aldol cyclisations leading to the generation of chiral compounds containing three contiguous stereocenters (Scheme 2.17).¹⁶⁵



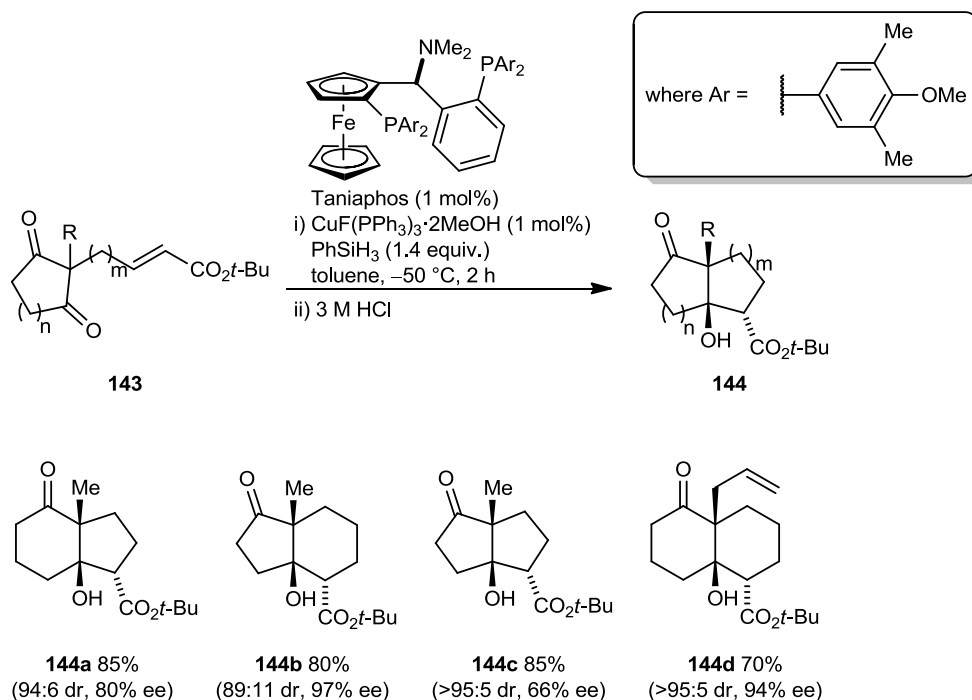
Scheme 2.17: Highly Diastereo- and Enantioselective Cu-Catalysed Aldol Cycloreductions

The copper-catalysed aldol cycloreduction was also performed using heterogeneous Cu/C in the presence of 10 mol% NaOPh and 4.0 equiv. of DEMS (dimethoxymethylsilane) in toluene at -10°C to afford the cyclised product **142a** with high enantioselectivity (Equation 2.4A). Alternatively, the process could also be run entirely in water despite the water-insoluble nature of adduct *Z*-**141a**. Thus, in the presence of nanomicelle-forming PTS (a nonionic, vitamin E based surfactant; 2% by weight), 1,4-reduction/cyclisation in the presence of excess PhSiH_3 at 5°C led to adduct *ent*-**142a** in comparable yield and ee (Equation 2.4B).



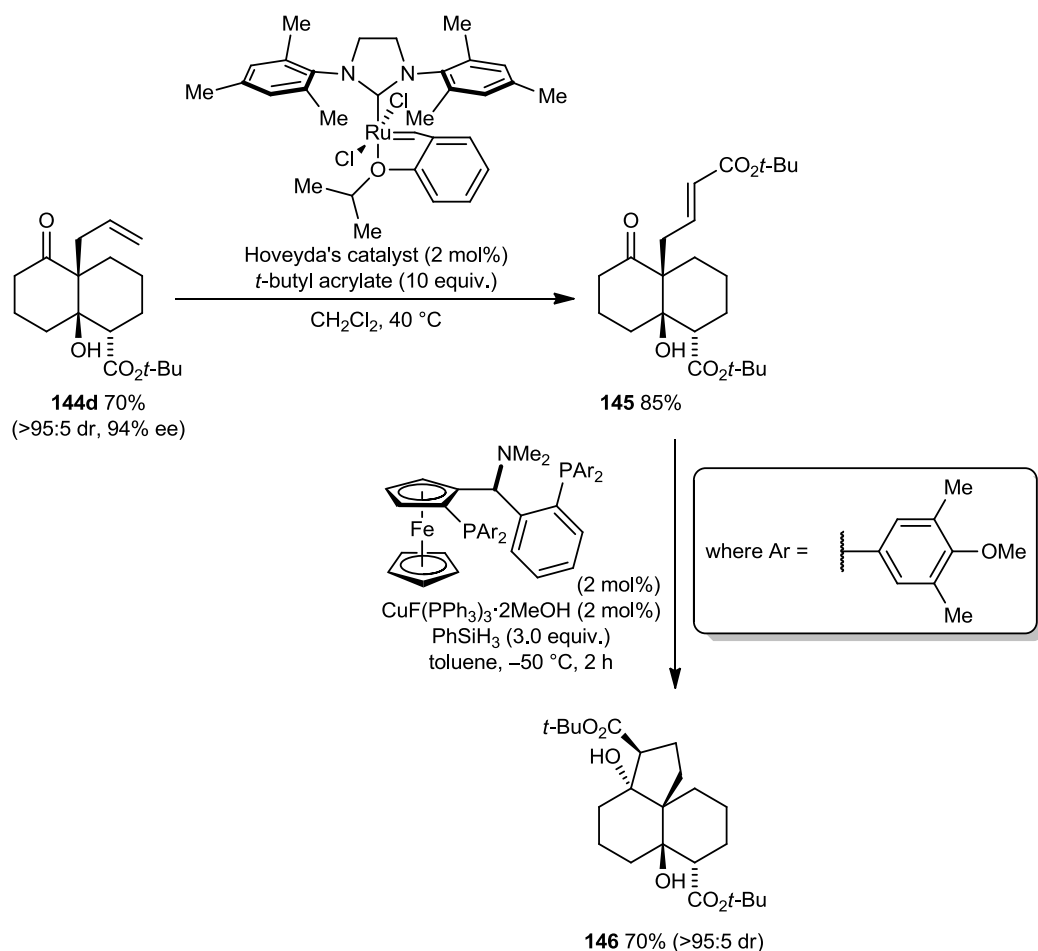
Equation 2.4: Heterogeneous and Aqueous Asymmetric Reductive Aldol Reactions

Riant and co-workers have reported the efficient construction of polycyclic derivatives through the CuH-catalysed aldol cycloreduction of diketoesters (Scheme 2.18).¹⁶⁶⁻¹⁶⁷ The intramolecular reductive aldol reaction proceeded smoothly yielding 5- and 6-membered bicyclic products with high diastereo- and enantioselectivities (products **144a-144d**). However, substrates bearing a longer tether that could generate 7- or 8-membered rings only resulted in simple reduction of the alkene.



Scheme 2.18: Enantioselective Cu-Catalysed Aldol Cycloreduction of Diketo-Esters

Substitution at the quaternary carbon of the cyclised precursors was possible. This enabled the construction of new angular tricyclic compounds, such as **146**, by using the allyl-substituted bicyclic adduct **144d** (Scheme 2.19). The cross metathesis of *t*-butyl acrylate and the allyl group of adduct **144d** was first carried out using sub-stoichiometric quantities of Hoveyda's second generation catalyst, affording the cyclisation precursor **145**. A second reductive aldol cyclisation of **145** was performed to generate the angular tricyclic adduct **146** as a single diastereomer in a good 70% isolated yield.



Scheme 2.19: Enantioselective Cu-Catalysed Aldol Cycloreduction for the Formation of Tricyclic Compounds

Marrubiin and marrubenol (Figure 2.4) are two natural diterpenes extracted from *Marrubium vulgare* L. (Horehound, Lamiaceae). The white horehound is a widespread Mediterranean plant used in traditional medicine, especially for its antinociceptive and expectorant effects. They have also been shown to exhibit potent relaxant activity.¹⁶⁸⁻¹⁷⁰ Mangoni and co-workers have reported the racemic synthesis of marrubiin in 24 steps starting from the Wieland-Miescher ketone.¹⁷¹ However, Riant and co-workers applied their reductive aldol cyclisation methodology to the enantioselective synthesis of a key intermediate *ent*-**151a** of these diterpenes (Scheme 2.20).^{167, 172}

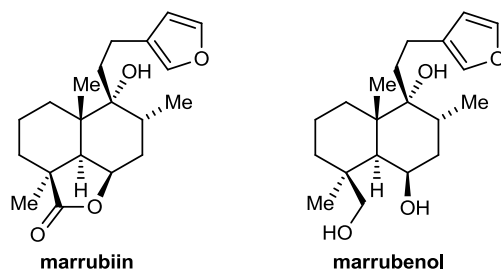
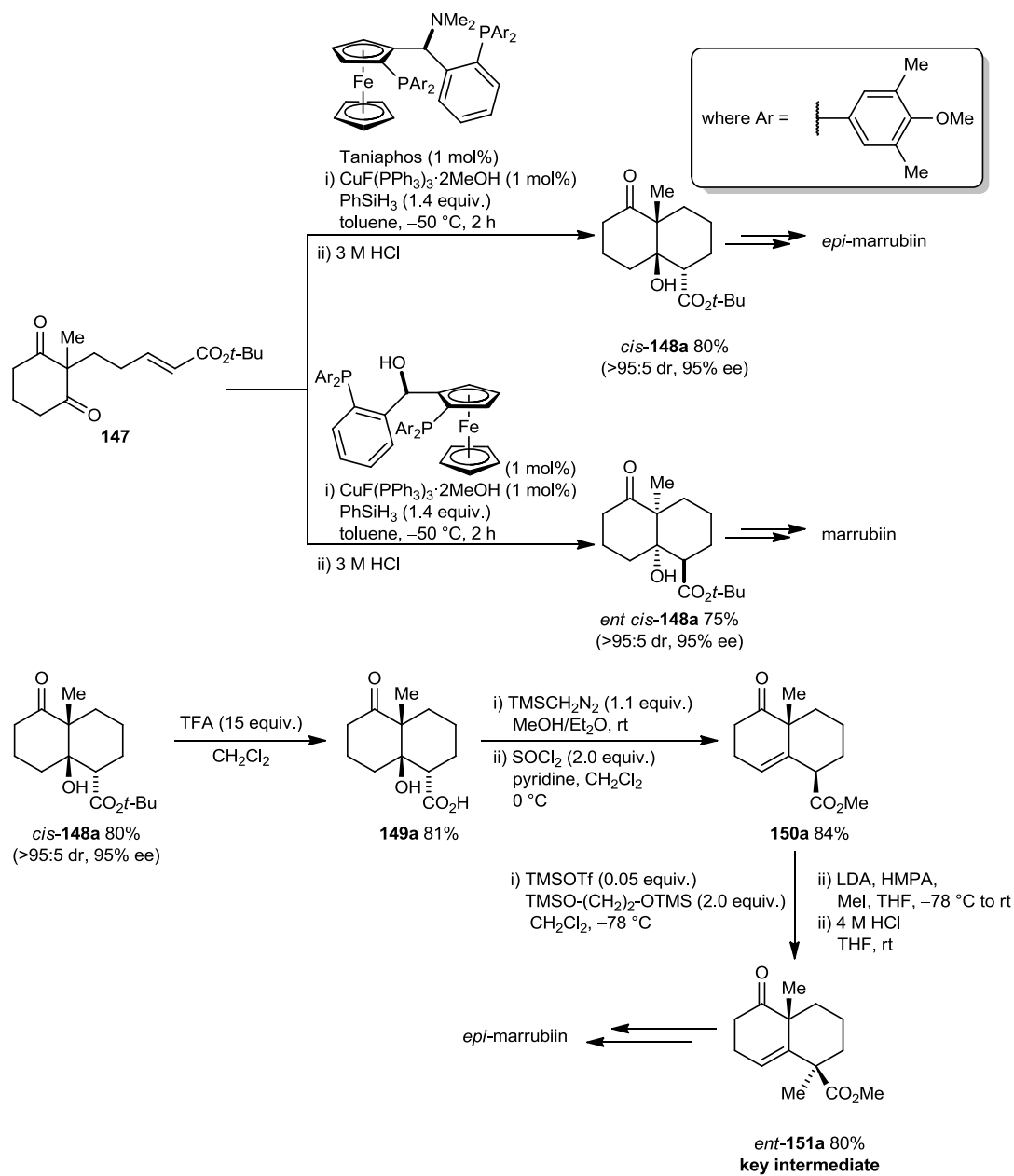
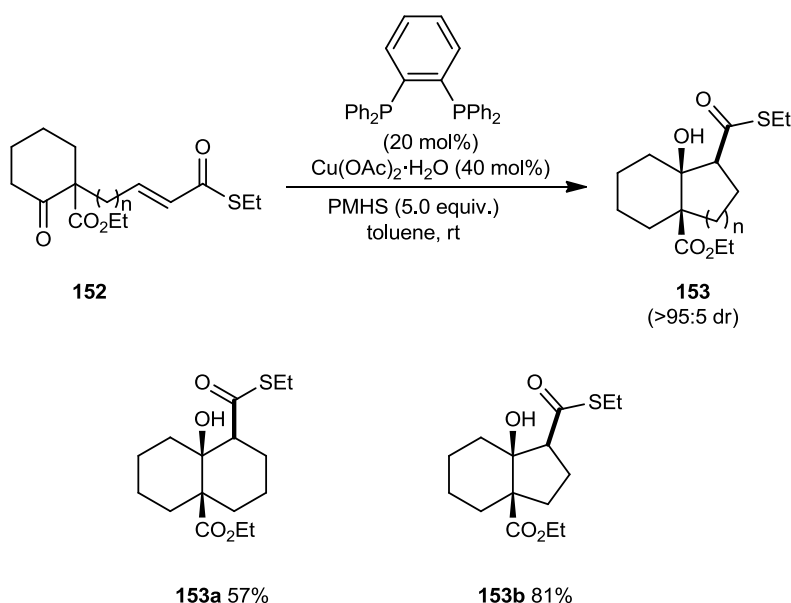


Figure 2.4: Structure of Marrubiin and Marrubenol



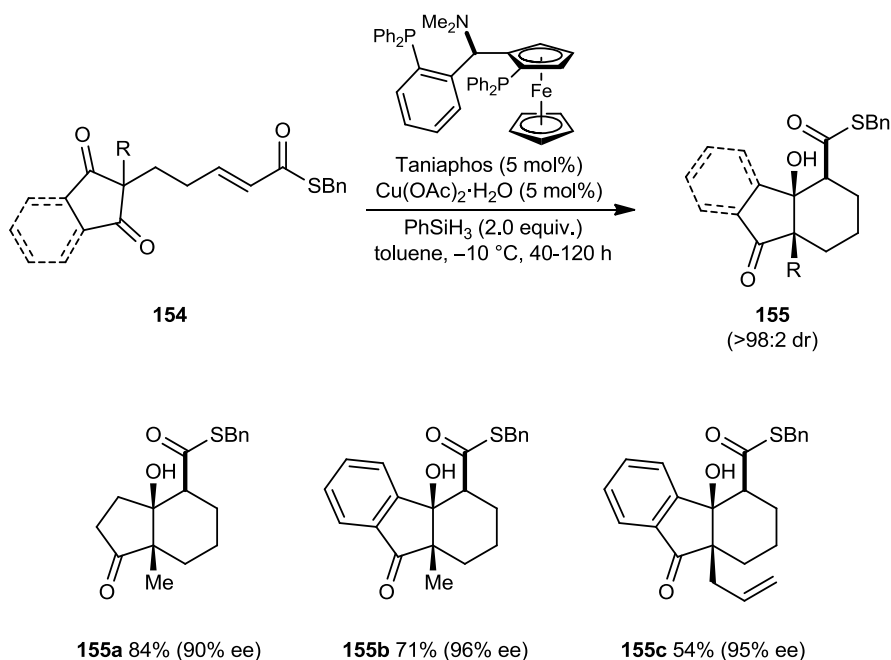
Scheme 2.20: Synthesis of Key Intermediate **ent-151a**

In nature, the reduction of α,β -unsaturated thioester derivatives, such as crotonyl ACP (acyl carrier protein), is a transformation in the fatty acid biosynthesis pathway. Yet, only a handful of reports exist in literature even for simple reduction of α,β -unsaturated thioesters. One possible reason for this is that sulfur-rich compounds have been known to poison several metal catalysts. However, Chiu and co-workers successfully developed the CuH-catalysed reductive aldol cyclisation of α,β -unsaturated thioesters with a tethered ketone (Scheme 2.21).¹⁷³ Disappointingly, only two cyclisations were reported (products **153a** and **153b**). Also, a high catalyst loading was required to achieve good conversion into the desired cyclised product.



Scheme 2.21: CuH-Catalysed Reductive Aldol Cyclisation of α,β -Unsaturated Thioesters

A subsequent report by Chiu and co-workers transformed this into an asymmetric process by employing a chiral bisphosphine ligand (Scheme 2.22).¹⁷⁴ In this report, products **155a-155c** were formed with excellent diastereo- and enantiocontrol. The catalyst loading was also reduced without affecting selectivity. The only obvious drawback was the long reaction times needed, which ranged from 40 to 120 hours. Nevertheless, the report successfully showed that diketo-enethioates could be used for CuH-catalysed reductive aldol cyclisations.

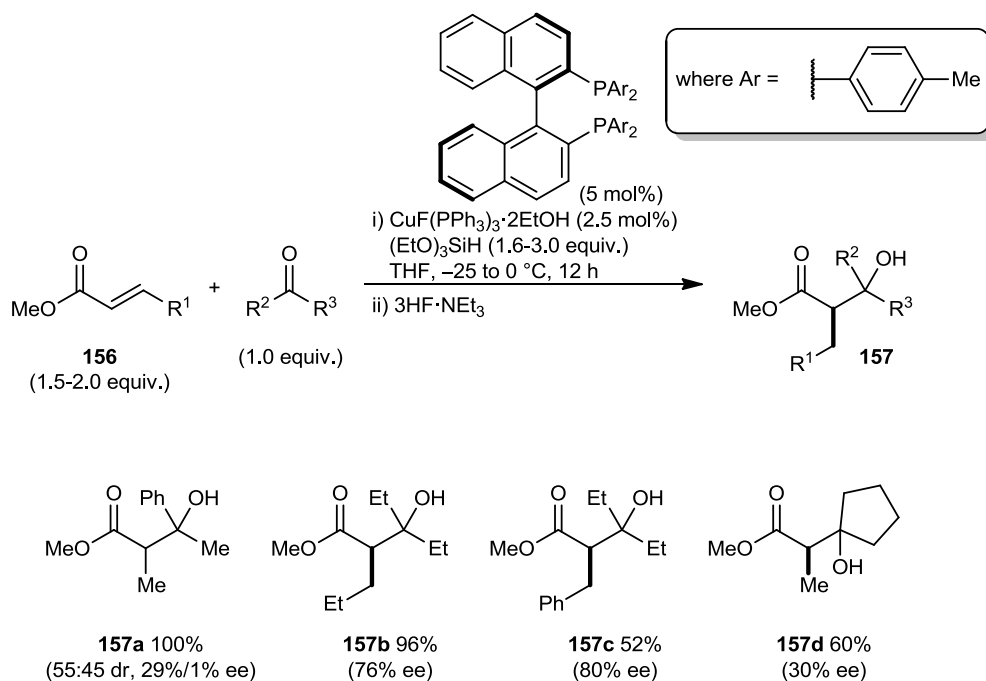


Scheme 2.22: Diastereo- and Enantioselective CuH-Catalysed Reductive Aldol Cyclisation of α,β -Unsaturated Thioesters

So far, enantioselective intramolecular reductive aldol cyclisations catalysed by chiral copper hydride species have been discussed, which proceed through the formation of entropically favoured medium-sized (5- or 6-membered) rings. The absence of this stabilising effect in analogous intermolecular reductive couplings can make such reactions less likely to occur. However, enantioselective CuH-catalysed intermolecular reductive aldol couplings using organosilanes as the source of hydride have also been reported previously.

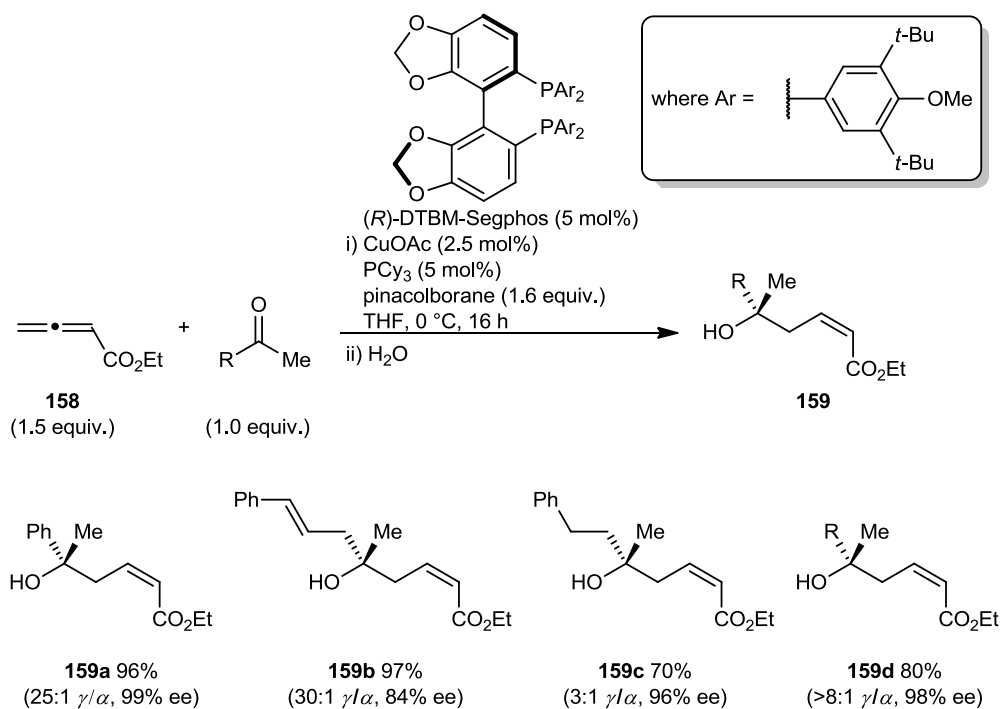
In 2006, Shibasaki and co-workers made initial attempts to reductively couple α,β -unsaturated esters with ketones using a chiral bisphosphine-ligated CuH species (Scheme 2.23).¹⁷⁵ Initially, methyl acrylate **156a** was reacted with a ketone possessing a prochiral carbonyl carbon such as acetophenone. Since high diastereo- and enantioselectivity was not observed (product **157a**), asymmetric induction was solely examined at the α -position using symmetrical ketones (products **157b-157d**). However, only modest enantioselectivities were observed. The use of cyclic ketones afforded the coupled product

157d with diminished enantioselectivity. Nevertheless, the report successfully demonstrated the intermolecular CuH-catalysed reductive coupling of enoates with ketones.



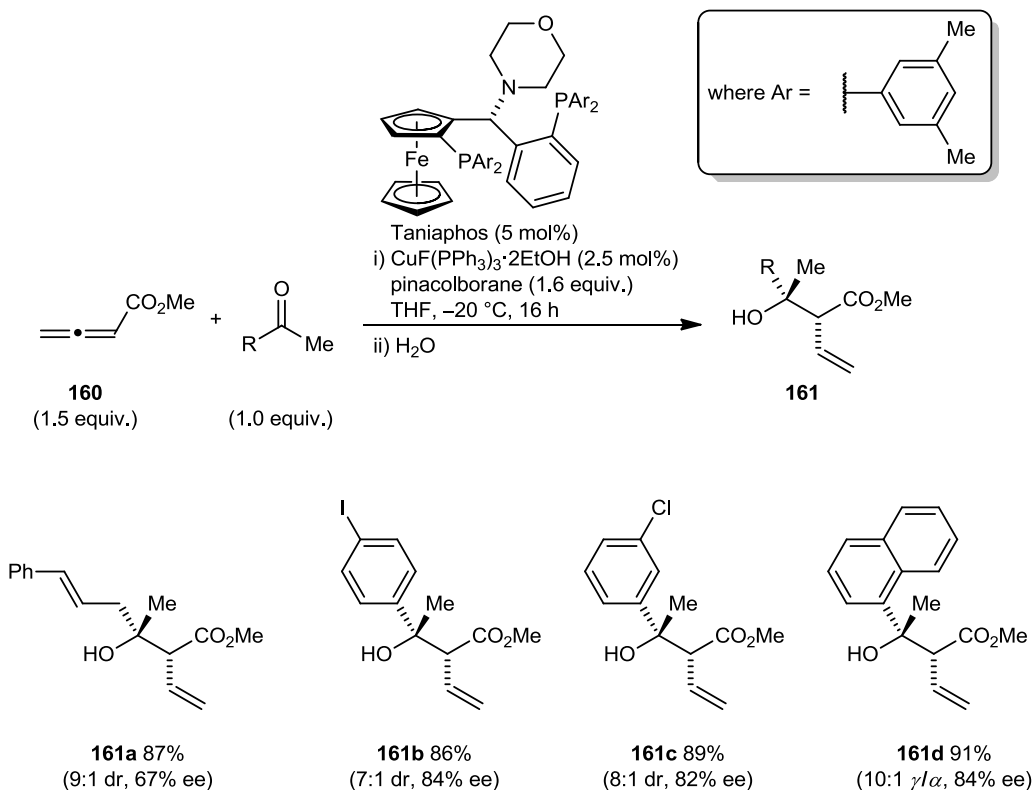
Scheme 2.23: Enantioselective Intermolecular Cu-Catalysed Reductive Aldol Coupling of Enoates with Ketones

Soon after, the same group also reported the reductive coupling of allenic esters to ketones (Scheme 2.24A and 2.24B).¹⁷⁶ The dramatic effect of the ligand was noted in this study whereby γ -*cis*- or α -selective products were formed depending on the ligand. In the presence of CuOAc (2.5 mol%), (*R*)-DTBM-Segphos (5 mol%), PCy_3 (5 mol%) and pinacolborane (1.6 equiv.) in THF allenic esters **158a-158d** reacted with various ketones to selectively produce enantioenriched γ -*cis*-products **159a-159d** (Scheme 2.24A).



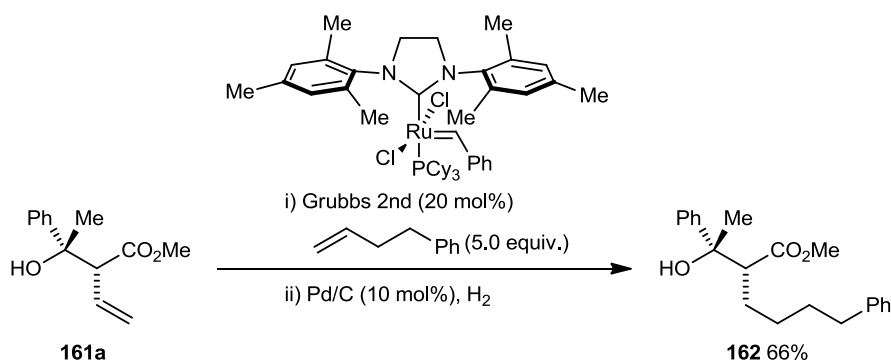
Scheme 2.24A: γ -*cis*-Selective Cu-Catalysed Reductive Coupling of Allenic Esters with Ketones

Interestingly, changing the reaction conditions to $\text{CuF(PPh}_3)_3 \cdot 2\text{EtOH}$ (2.5 mol%), Taniaphos ligand (5 mol%) and pinacolborane (1.6 equiv.) in THF led to the selective production of the α -products **161a-161d** in modest to high enantioselectivity (Scheme 2.24B). Although the product constitution (α - or γ -aldol) could be switched depending on the structure of the chiral bisphosphine ligand, no explanation of the reaction mechanism and how the choice of ligand affects product outcome was provided.



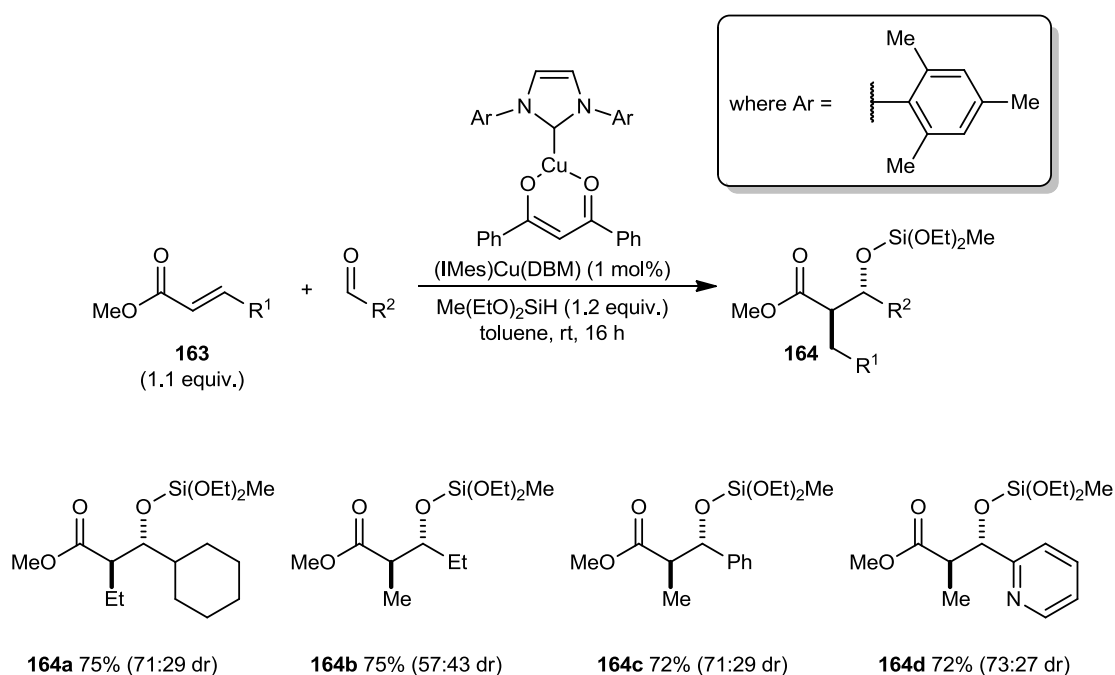
Scheme 2.24B: α -Selective Cu-Catalysed Reductive Coupling of Allenic Esters with Ketones

The existence of a terminal olefin in products **161a-161d** allowed further conversion to various α -substituted aldol products using a cross-metathesis reaction. For example, **161a** was converted to **162** containing a longer alkyl chain at the α -position without epimerisation (Scheme 2.25).



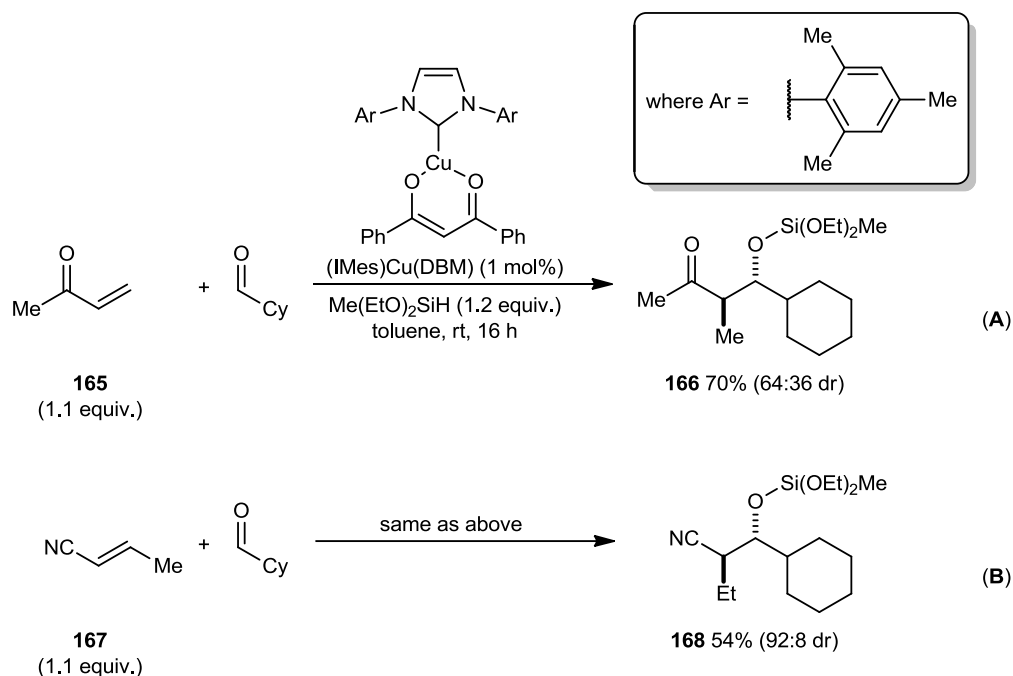
Scheme 2.25: Typical Conversion of α -Vinyl Aldol Product

In the same year, Riant and co-workers also reported the reductive aldol coupling of α,β -unsaturated esters with various aldehydes using sub-stoichiometric quantities of an achiral NHC-ligated copper catalyst (Scheme 2.26).¹⁷⁷ The main drawback of (NHC)CuX complexes is the mandatory use of an activator such as NaOt-Bu. This permits a halide–alkoxide exchange on the copper atom, which in turn can react with the hydrosilane to generate the copper–hydride active species. To avoid the use of an activator, air-stable (IMes)Cu(dibenzoylmethanoate) complex was synthesised and then used to catalyse reductive aldol reactions. The choice of the co-ligand on the metal center was made on the assumption that a weak Cu–O bond would allow direct activation of the complex to generate the desired copper–hydride catalyst. The diastereoselectivities observed were modest, but the chemoselective nature of the reaction was remarkable.



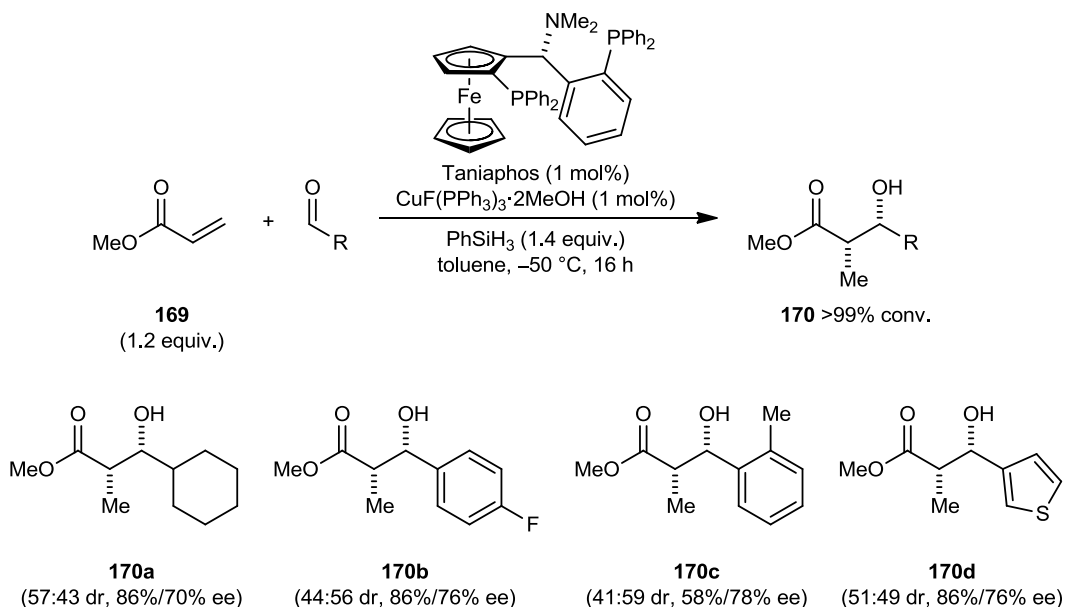
Scheme 2.26: Intermolecular NHC-Ligated Cu-Catalysed Reductive Aldol Coupling of Enoates with Aldehydes

The use of other functional groups such as a ketone (substrate **165**) and a nitrile (substrate **167**) for activating the adjacent alkene toward CuH-catalysed reductive couplings (Equation 2.5A and 2.5B, respectively) was also demonstrated in the same report.



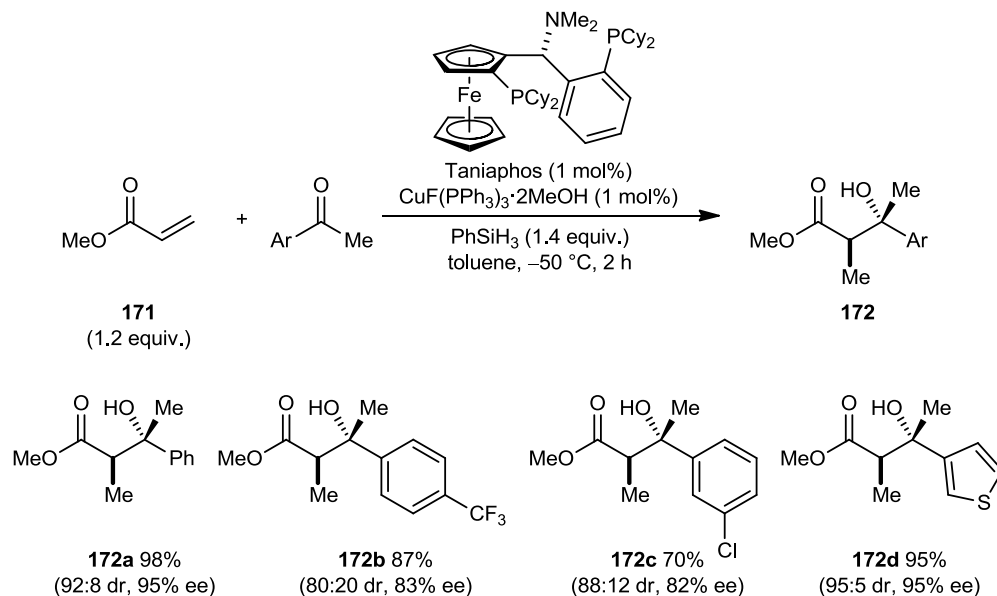
Equation 2.5: Cu-Catalysed Reductive Coupling of Enones or Cyanoalkenes with Aldehydes

Riant and co-workers also reported the enantioselective CuH-catalysed reductive coupling of α,β -unsaturated esters with various aldehydes by employing a chiral bisphosphine ligand (Scheme 2.27).¹⁷⁸⁻¹⁷⁹ Poor diastereoselectivity and modest enantioselectivities were observed. However, given the high reactivity of aldehydes toward CuH-catalysed 1,2-reduction, the ability to selectively reduce the α,β -unsaturated ester and then couple it with an aldehyde is appreciable. Oddly, the paper did not report any isolated yields for products **170a-170d**.



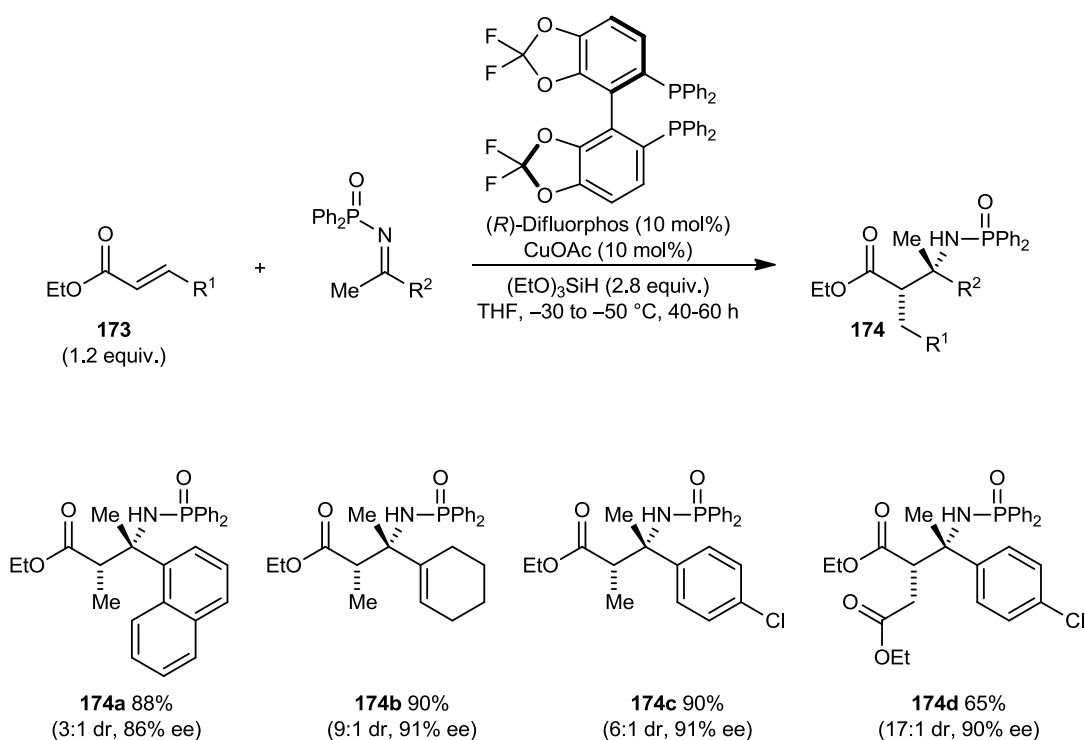
Scheme 2.27: Cu-Catalysed Reductive Coupling of Enoates with Aldehydes

The reductive aldol reactions previously described by Riant did not provide the coupled products in high diastereo- and enantioselection. This was overcome in their subsequent publication, which reported the CuH-catalysed reductive coupling of α,β -unsaturated esters with ketones affording products **172a-172d** with high diastereo- and enantiocontrol (Scheme 2.28).¹⁸⁰⁻¹⁸¹



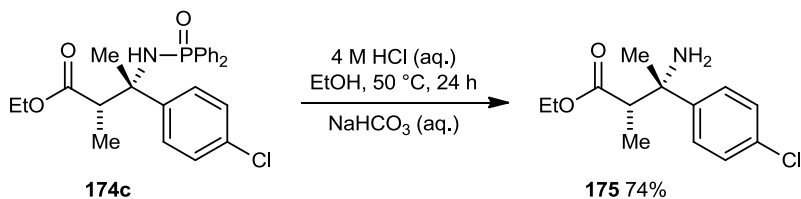
Scheme 2.28: Cu-Catalysed Reductive Coupling of Enoates with Ketones

Shibasaki and co-workers have also demonstrated the use of CuH catalysis in reductive Mannich-type reactions, thereby showing that the scope of the electrophile is not limited to aldehydes and ketones (Scheme 2.29).¹⁸² A high catalyst loading of 10 mol% and the addition of 2.8 equiv. of (EtO)₃SiH were needed for this process. Diastero- and enantioselectivities were high in most cases (products **174a-174d**).



Scheme 2.29: Enantioselective Intermolecular Cu-Catalysed Reductive Mannich Reaction of Enoates with Ketimines

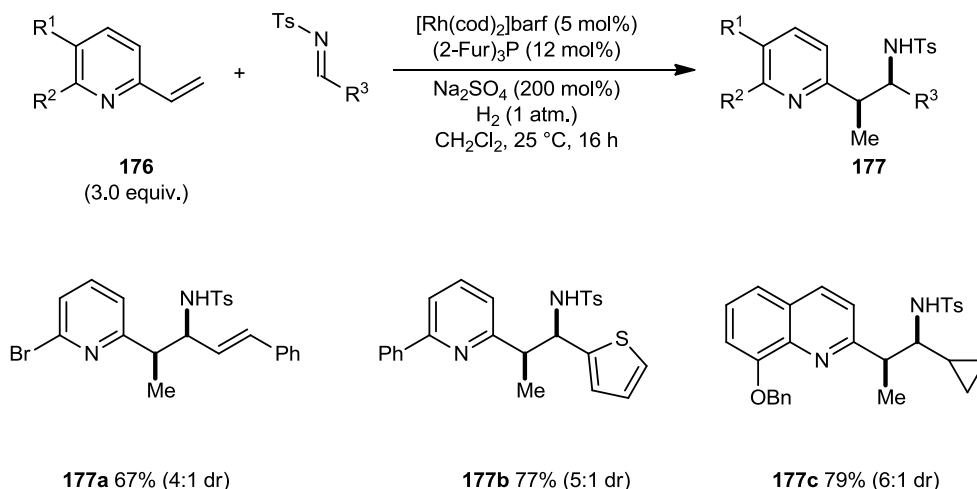
The synthetic utility of the process was also demonstrated by the conversion of the reductive Mannich product **174c** into enantioenriched β -amino acid derivative **175** in high yield without any epimerisation through cleavage of the diphenylphosphinoyl group under acidic conditions (Equation 2.6).



Equation 2.6: Conversion to β -Amino Acid Derivative

Examples of CuH-catalysed tandem processes, specifically those involving the 1,4-reduction of polarised alkenes and their subsequent trapping with an electrophile, are present in literature and have been discussed so far. Our group set about to extend this methodology to include other important, yet underexploited electron-withdrawing groups on the acceptor. Drawing from past knowledge that azaarenes containing a suitably position C=N moiety could active adjacent alkenes toward CuH-catalysed conjugate reductions,¹⁰² we questioned whether the intermediate organocopper species formed could be trapped by an electrophile such as an aldehyde or a ketone to afford the reductively coupled product (Equation 2.7).

To the best of our knowledge, the only report of catalytic reductive coupling of alkenylazaarenes has appeared from Krische's group, who described a racemic rhodium-catalysed hydrogenative coupling^{153, 183-187} of vinylazines with *N*-sulfonylaldimines (Scheme 2.30).¹⁸⁸

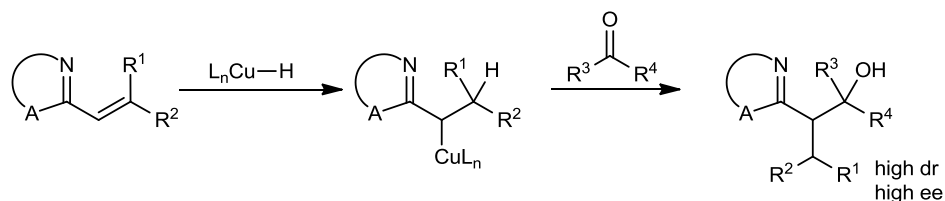


Scheme 2.30: Reductive Coupling of Vinylazines with Imines via Rh-Catalysed Hydrogenation

The ability to couple vinylazines with imines using molecular hydrogen delivered at 1 atmospheric pressure at room temperature is remarkable. The addition of Na₂SO₄ was found to suppress imine hydrolysis. Whereas the parent 2-vinylpyridine did not participate in the coupling, presumably due to strong coordination at nitrogen, 6-substituted-2-vinyl pyridines **176a-176c** coupled efficiently to (hetero)aromatic and aliphatic imines. Products **177a-177c** were obtained in good diastereoselectivity. However, the use of rhodium, which is an expensive metal, and the generation of optically inactive products were some of the limitations encountered in their report, which our group hoped to address.

2. Results and Discussion

Work in our group thus began in order to examine whether 2-alkenylazaarenes could be reductively coupled with ketones in an asymmetric fashion by employing a cheap metal such as copper (Equation 2.7).

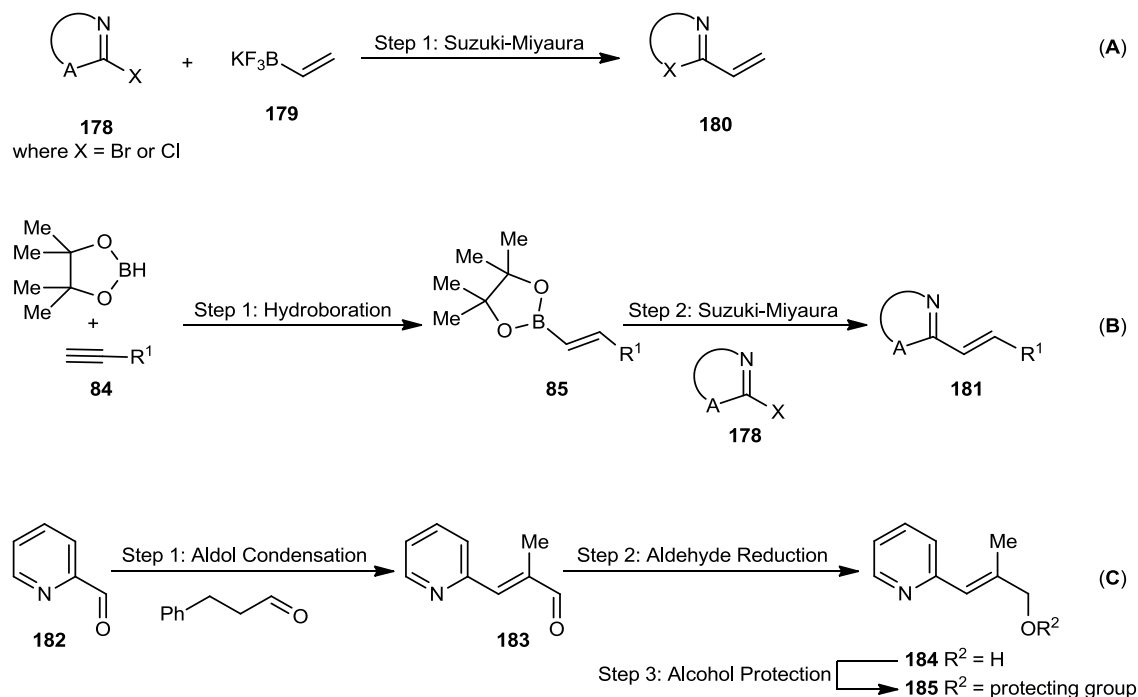


Equation 2.7: Cu-Catalysed Reductive Coupling of 2-Alkenylazaarenes with Ketones

Prior to testing our theory, synthesis of the appropriate substrates was needed and is presented below. All work was done with the help of Bonnie Choi, who is a current member of our group.

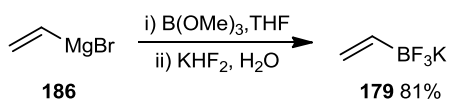
2.1. Preparation of 2-Alkenylazaarenes

Various 2-vinylazaarenes, β -substituted and β,β -disubstituted 2-alkenylazaarenes were synthesised in our lab following general procedures as illustrated in Scheme 2.31A-2.31C, respectively.



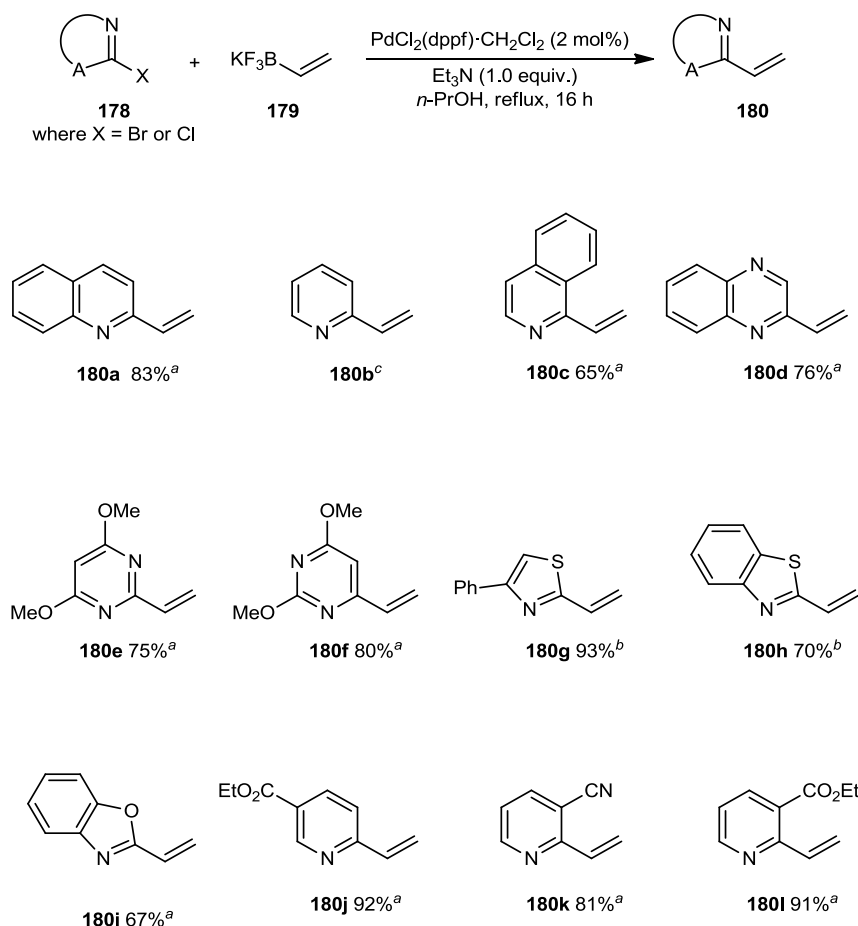
Scheme 2.31: Strategy for the Synthesis of Alkenylazaarenes

Despite being commercially available, potassium vinyltrifluoroborate **179** was conveniently prepared in our lab through addition of vinyl magnesium bromide **186** to trimethyl borate and *in situ* treatment of the resulting boronic ester with KHF_2 (Equation 2.8).¹⁸⁹⁻¹⁹⁰



Equation 2.8: Preparation of Potassium Vinyltrifluoroborate

Next, following standard Suzuki-Miyaura reaction conditions various azaaryl halides **178** were coupled with potassium vinyltrifluoroborate **179** in the presence of a palladium catalyst and base (Scheme 2.32A). The 2-vinylazaarenes were obtained in high yields (product **180a** and products **180c-180l**).

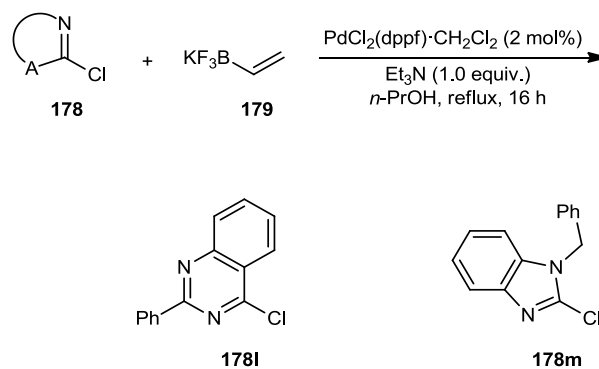


^a Reaction was conducted using azaaryl chloride **178**. ^b Reaction was conducted using azaaryl bromide **178**.

^c Reagent was purchased from commercial sources.

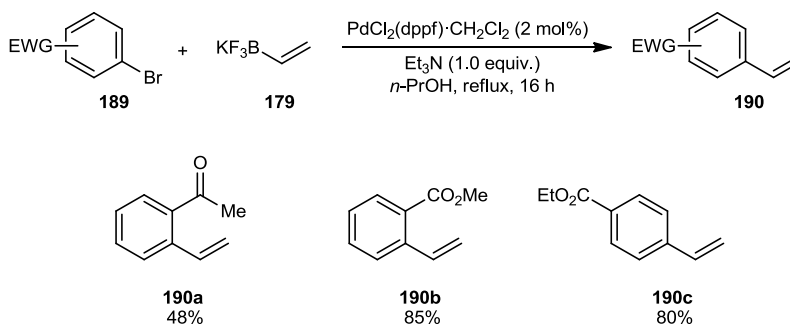
Scheme 2.32A: Synthesis of 2-Vinylazaarenes

Azaaryl halides **178l** and **178m** failed to couple with potassium vinyltrifluoroborate under our standard conditions, presumably due to high steric demand (Scheme 2.32B).



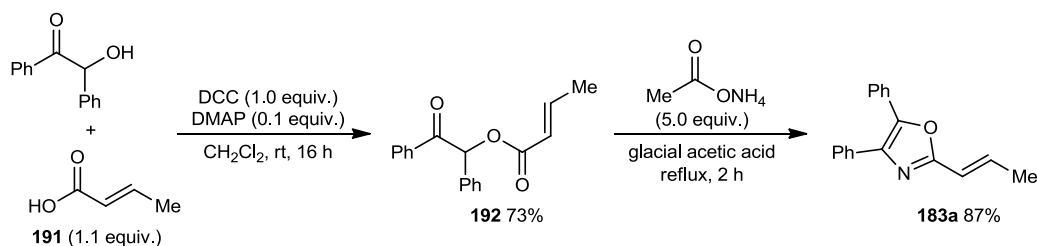
Scheme 2.32B: Synthesis of 2-Vinylazaarenes

Similarly, 2-vinylarenes containing electron-withdrawing substituents were also prepared (Scheme 2.33). Drawing from our previous study on rhodium-catalysed conjugate arylations (Chapter 1), we hoped that arenes containing electron-withdrawing substituents may activate the adjacent alkene, thereby allowing such substrates to participate in transition metal-catalysed reductive aldol couplings.



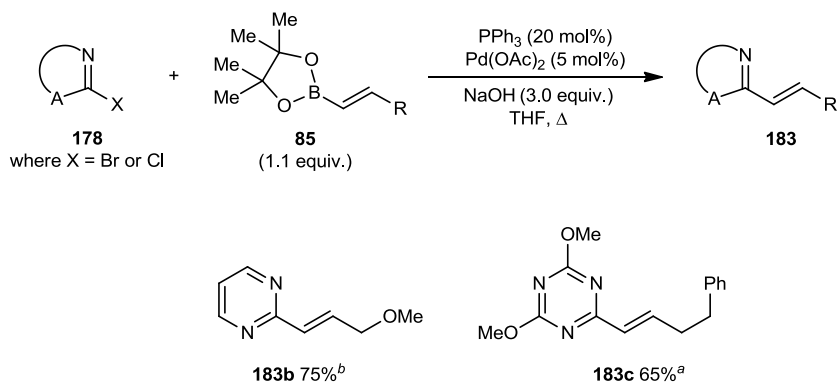
Scheme 2.33: Synthesis of 2-Vinylarenes

For the preparation of β -substituted 2-alkenylazaarenes, the reaction of benzoin with crotonic acid **191** in the presence of DMAP and DCC afforded intermediate **192**, which upon treatment with ammonium acetate in glacial acetic acid provided the desired 2-alkenylloxazole **183a** (Scheme 2.34). Product **183a** was synthesised by Iain Roy, who is a current member of our group.



Scheme 2.34: Synthesis of β -Substituted 2-Alkenyloxazole

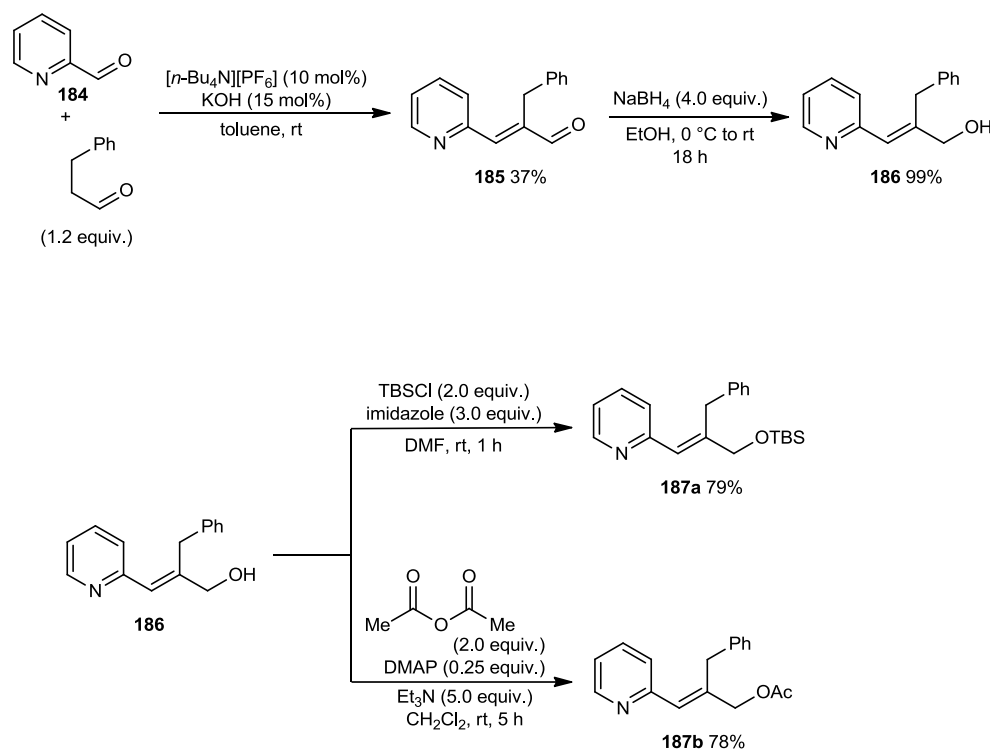
Other β -substituted 2-alkenylazaarenes were prepared by coupling alkenylboronic acid pinacol esters, prepared from our previous study (Chapter 1), with azaaryl halides following standard Suzuki-Miyaura coupling conditions (Scheme 2.35).



^a Reaction was conducted using azaaryl chloride **178**. ^b Reaction was conducted using azaaryl bromide **178**.

Scheme 2.35: Synthesis of β -Substituted 2-Alkenylazaarenes by Suzuki-Miyaura Coupling

Lastly, two β,β -disubstituted 2-alkenylazaarenes were also synthesised. This was achieved by a cross-aldol condensation reaction of picolinaldehyde **184** with 3-phenylpropanal to produce enal **185**. Reduction of the aldehyde in compound **185** to the corresponding alcohol **186** and subsequent protection of the alcohol afforded the desired trisubstituted 2-alkenylazaarenes **187a** and **187b** in good yield (Scheme 2.36).

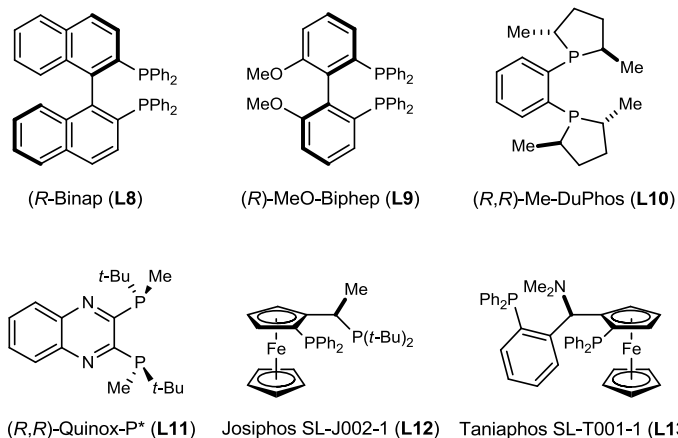
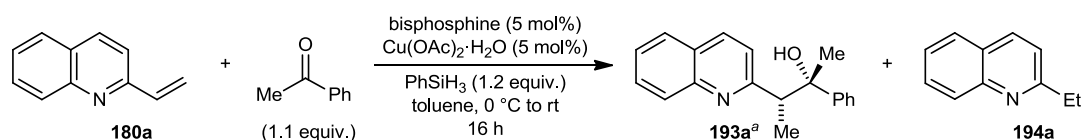


Scheme 2.36: Synthesis of β,β -Disubstituted 2-Alkenylazaarenes

With the 2-alkenylazaarenes in hand, we began to investigate the possibility of our substrates undergoing CuH-catalysed reductive aldol couplings with ketones.

2.2. Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes with Ketones

This study began with examination of the enantioselective reductive coupling of 2-vinylquinoline **180a** with commercially available acetophenone (1.1 equiv.) using PhSiH_3 (1.2 equiv.) as the hydride source, 5 mol% $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and 5 mol% of various chiral bisphosphine ligands in toluene (Table 2.1).



Entry	Ligand	193a:194a ^b	dr	ee (%) ^c
1	L8	11:1	1:1	43/50
2	L9	13:1	1:1	67/67
3	L10	24:1	1:1	27/17
4	L11	17:1	1:1	−60/−92
5	L12	12:1	1:1	92/93
6	L13	7:1	5:1	93/60

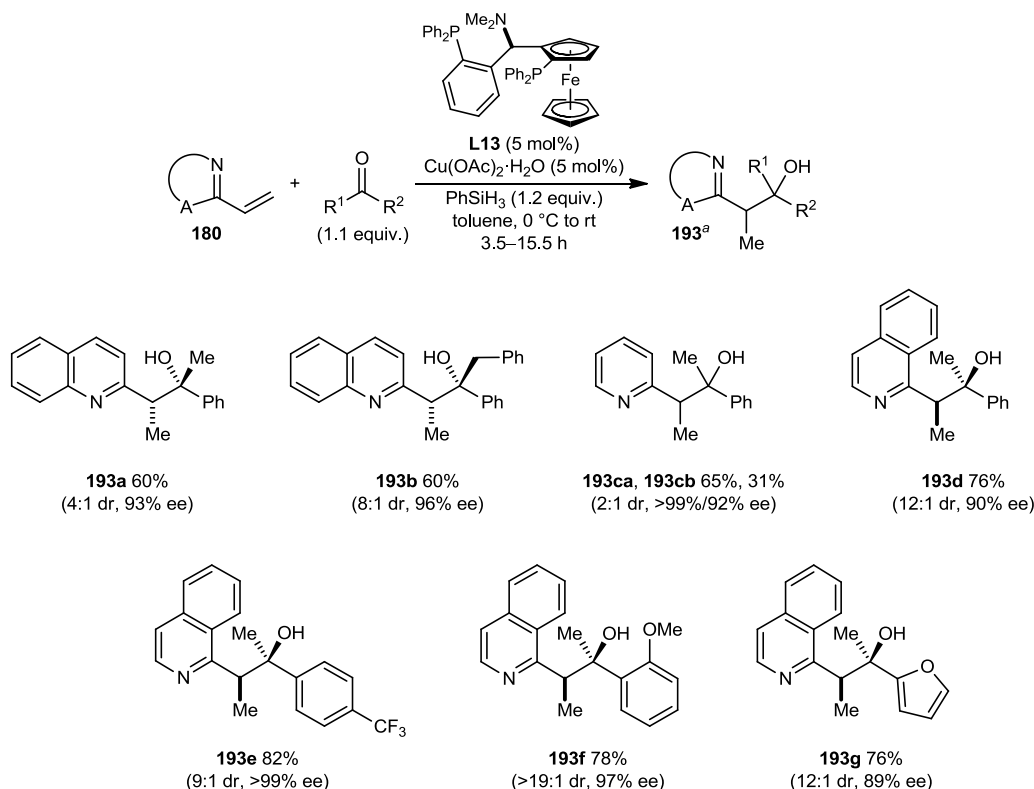
^a Reactions were conducted using 0.10 mmol of **180a**. ^b Determined by ¹H NMR analysis of the unpurified reaction mixtures. ^c Determined by chiral HPLC analysis.

Table 2.1: Evaluation of Chiral Bisphosphines

Apart from high diastereo- and enantioselection, good chemoselectivity (ratio of **193a:194a**) was also our goal. Pleasingly, proof of concept was quickly established, and all ligands evaluated led to complete consumption of **180a** to provide the coupling product **193a** as a mixture of diastereomers, along with traces of the simple reduction product **194a**. Enantioselectivities were modest using ligands **L8-L10** (entries 1-3), but high using *(R,R)*-Quinox-P* (**L11**) (entry 4), the Josiphos ligand **L12** (entry 5), and the Taniaphos ligand **L13** (entry 6). However, no diastereoselectivity was observed in most cases, with the notable exception being the reaction using **L13** which provided **193a** in 5:1 dr and 93% ee for the major isomer while also displaying good chemoselectivity (entry 6). Accordingly, **L13** was selected for further experimentation.

PhSiH₃ was chosen as the stoichiometric source of hydride in our study. Using TMDS, PMHS, and Ph₂MeSiH displayed comparable enantioinduction; however, slower reaction rates were observed with these hydrosilanes. In most cases significant quantities of the starting 2-vinylquinoline **180a** was also recovered. The use of (EtO)₃SiH led to decomposition of the starting material.

With respect to the solvent; acetone, CH₂Cl₂, THF, Et₂O and dioxane afforded product **193a** in diminished diastereoselectivity as compared to the 5:1 dr observed with the use of toluene. The use of a 1:1 mixture of THF in toluene did not improve diastereoselectivity either. Therefore, toluene was confirmed as the preferred solvent for this process.

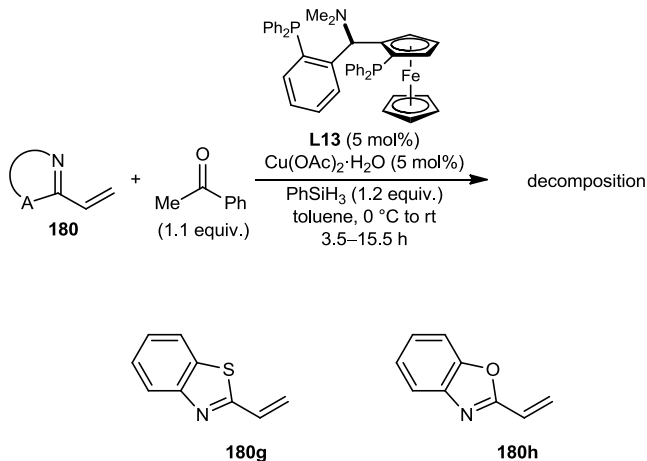


^a Reactions were conducted using 0.30–0.40 mmol of **180**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

Scheme 2.37A: Reductive Aldol Coupling of Vinylazaarenes with Acyclic Ketones

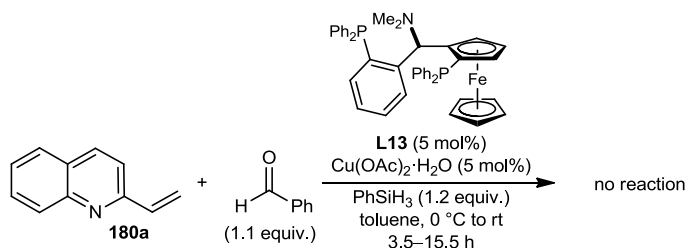
Next, the scope of our reaction was tested by subjecting our previously prepared 2-alkenylazaarenes to the optimised conditions. Results of reductive coupling of various 2-vinylazaarenes with a range of acyclic ketones are presented in Scheme 2.37A. Effective substrates included azines such as quinoline (products **193a** and **193b**), pyridine (product **193c**) and isoquinoline (products **193d-193g**). With acyclic ketones, the diastereoselectivity of the reaction appears to be dependent on the steric properties of the azaarene, with diastereoselectivity increasing from pyridine to quinoline to isoquinoline (compare diastereomeric ratios for products **193c**, **193a**, and **193d**). In the coupling of 2-vinylpyridine with acetophenone, the two diastereomeric products **193ca** and **193cb** were isolated with high enantioselectivities (>99% and 92% ee, respectively). Regarding the electrophile, the process is tolerant of acyclic ketones containing various alkyl, aryl, or heteroaryl substituents (products **193a-193g**). Ketones containing electron-withdrawing (**193e**) or electron-donating (**193f**) substituents on the aryl ring also readily coupled with vinylazaarenes under our reaction conditions.

Azole-containing substrates **180g** and **180h** decomposed into a mixture of unidentifiable products under our reductive coupling conditions, as shown in Scheme 2.37B.



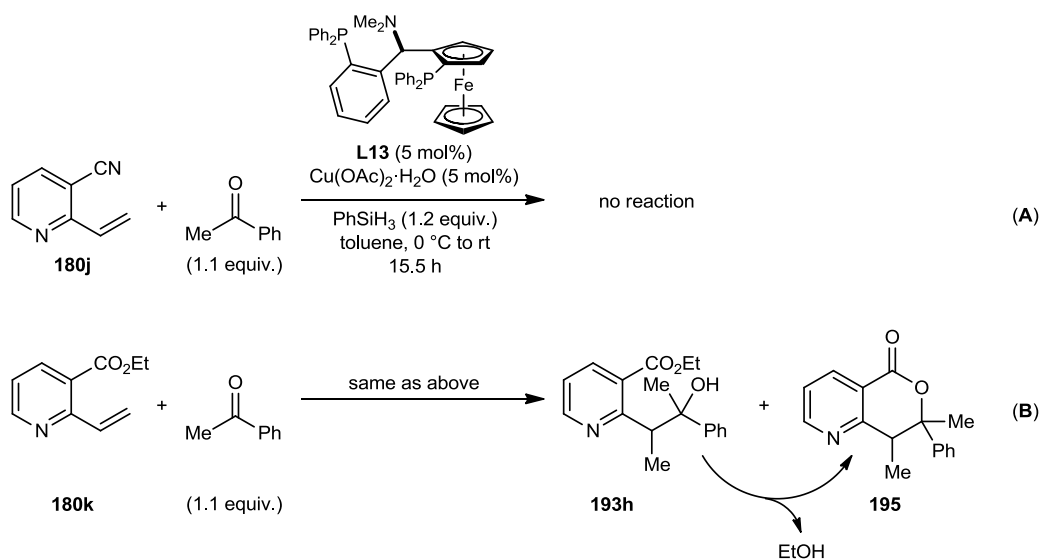
Scheme 2.37B: Reductive Aldol Coupling of Vinylazaarenes with Acyclic Ketones

While 2-vinylazaarenes coupled smoothly with various acyclic ketones, 2-vinylquinoline **180a** failed to react with benzaldehyde (Equation 2.9). This was attributed to the preferential reduction of benzaldehyde to benzyl alcohol.



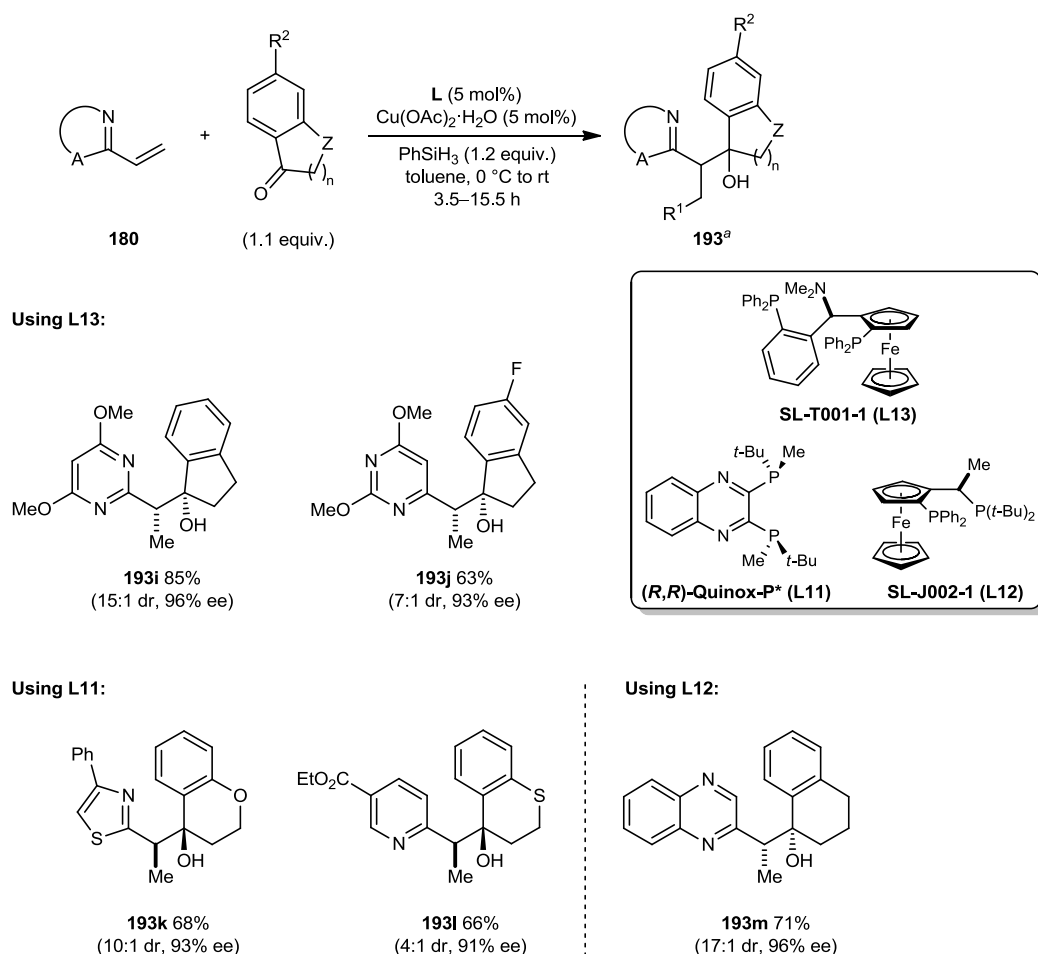
Equation 2.9: Reductive Coupling of 2-Vinylquinoline with Benzaldehyde

Interestingly, while substrate **180j** failed to couple with acetophenone leading to the generation of a mixture of unidentifiable products (Equation 2.10A), the analogous substrate **180k** did undergo an intermolecular reductive coupling with acetophenone followed by partial intramolecular cyclisation of **193h** to form **195** (Equation 2.10B). Unfortunately, a 1:1 mixture of **193h** to **195** was confirmed by ^1H NMR spectroscopy. Running the reaction at an elevated temperature of 50 °C in the hope of biasing it toward the formation of a single product (either **193h** or **195**) proved to be unsuccessful and the reaction was eventually abandoned.



Equation 2.10: Reductive Aldol Coupling of 3-Substituted Vinylazaarenes with Acetophenone

Apart from acyclic ketones, 5- and 6-membered cyclic ketones served as effective coupling partners for our reductive aldol process (Scheme 2.38), as exemplified by the successful use of two indanones (products **193i** and **192j**), 4-chromanone (product **193k**), 4-thiochromanone (product **193l**), and tetralone (product **193m**). These results also broadened the scope of the azaarene to include two isomeric forms of pyrimidine (products **193i** and **193j**), a thiazole (**193k**), a 5-substituted pyridine (**193l**) and a quinoxaline (**193m**).

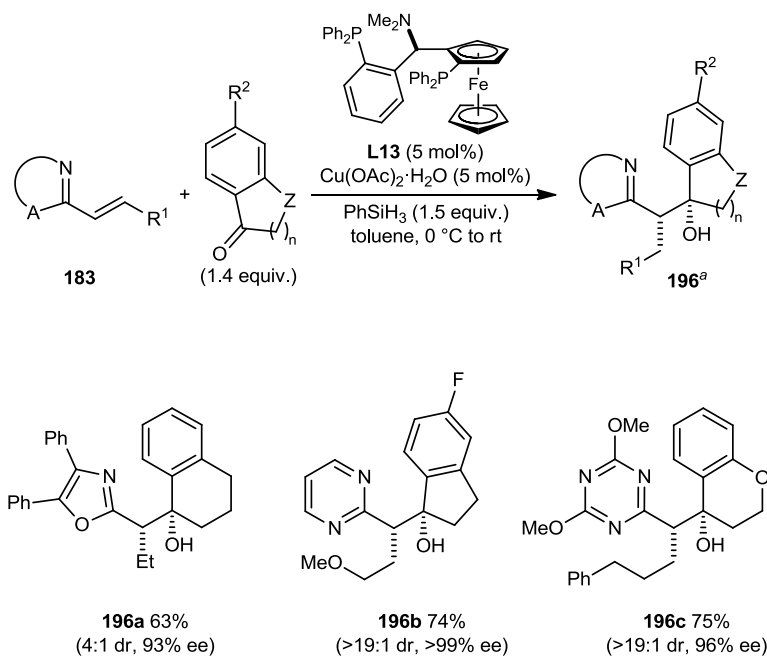


^a Reactions were conducted using 0.30–0.40 mmol of **180**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

Scheme 2.38: Reductive Aldol Coupling of Vinylazaarenes with Cyclic Ketones

Although **L13** provided the best results for products **193i** and **193j**, this ligand resulted in a low yield in the attempted synthesis of **193k**, and poor diastereo- and enantioselectivities in the attempted syntheses of **193l** and **193m**. In these cases, (*R,R*)-Quinox-P* (**L11**) was superior for **193k** and **193l**, and the Josiphos ligand **L12** was optimal for **193m**.

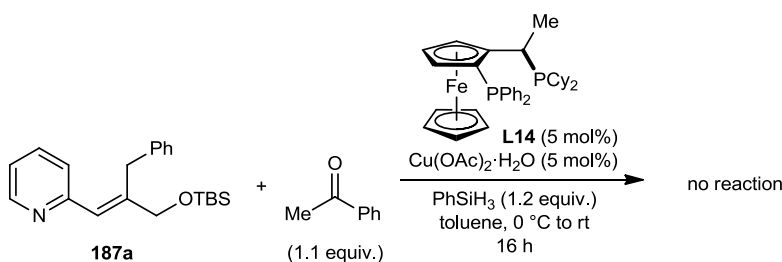
The process was not limited to vinylazaarenes; β -substituted alkenylazaarenes were also effective coupling partners (Scheme 2.39). For example, alkenylazaarenes **183a-183c** containing methyl, allylic ether, or phenethyl groups smoothly underwent reductive coupling to deliver products **196a-196c** in high diastereo- and enantioselectivities. Furthermore, these products contain additional examples of azaarenes such as a diphenyloxazole (product **196a**), a pyrimidine (product **196b**) and a dimethoxytriazine (product **196c**).



^a Reactions were conducted using 0.30 mmol of **183**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

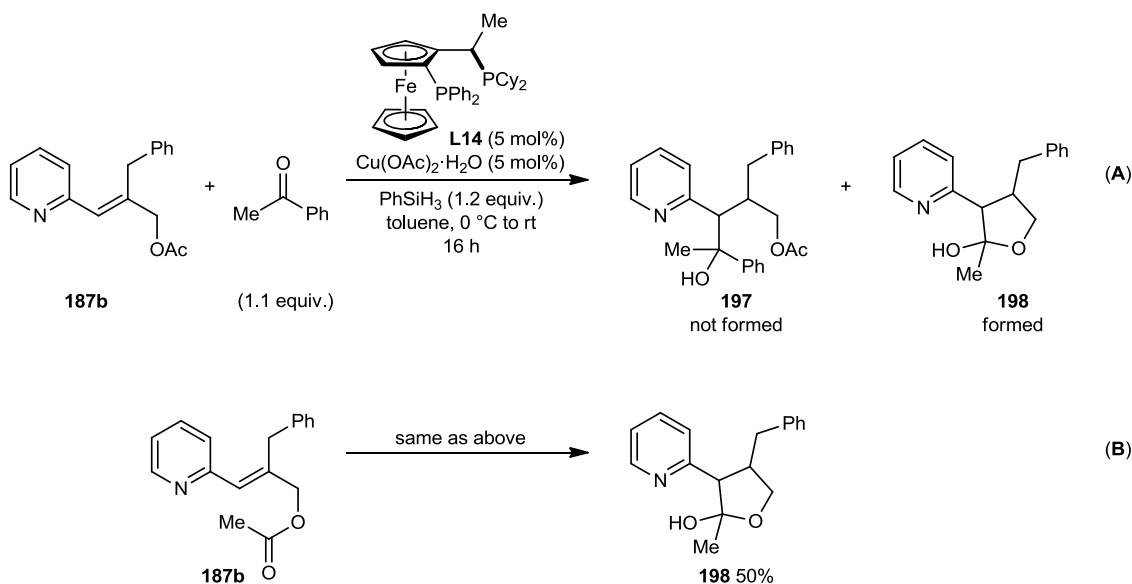
Scheme 2.39: Reductive Aldol Coupling of β -Substituted 2-Alkenylazaarenes with Ketones

β,β -Disubstituted 2-alkenylazaarenes were also tested with the aim of generating three contiguous stereocenters through an intermolecular enantioselective CuH-catalysed reductive coupling. First, substrate **187a** was reacted with acetophenone under our developed methodology (Equation 2.11). However, no coupled product was observed. The high steric congestion at the β -site may explain the failure of substrate **187a** to reductively couple with acetophenone.



Equation 2.11: Reductive Coupling of **187a** with Acetophenone

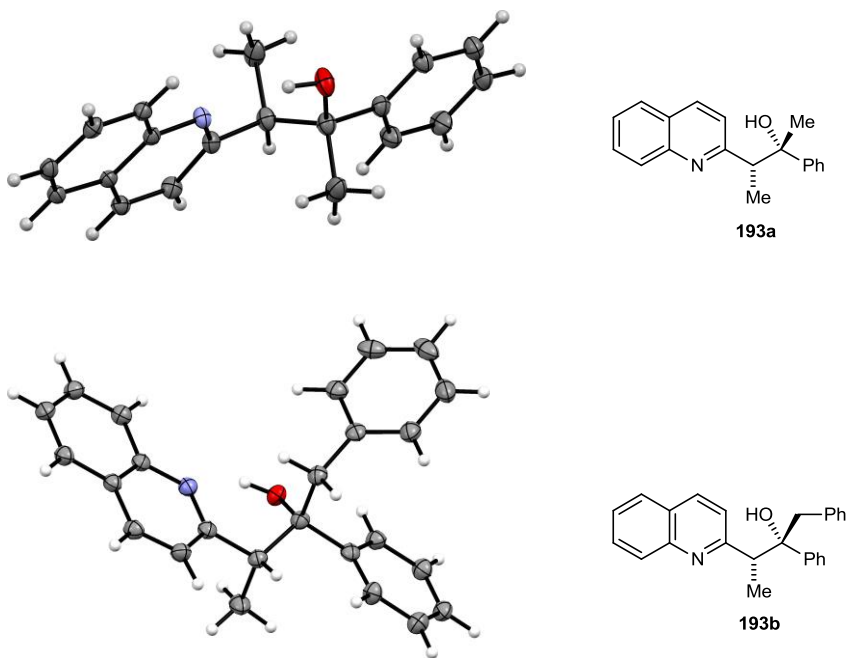
Interestingly, when substrate **187b** was reacted with acetophenone under the same conditions, significant quantities of the reductive aldol cyclisation product **198** was observed without any evidence of the intermolecular reductive coupling product **197** being formed (Equation 2.12A).



Equation 2.12: Reductive Aldol Cyclisation of **187b**

The formation of **198** shown in Equation 2.12A highlights the preference of substrate **187b** to undergo an entropically-favoured reductive cyclisation with a tethered ester group instead of reductively coupling with the more electrophilic ketone. Conducting the reaction in the absence of acetophenone afforded the hemiketal **198** as the sole product, which was isolated in a moderate 50% yield (Equation 2.12B). The reaction to generate *rac*-**198** by employing a variety of achiral ligands failed. Therefore, the ee of product **198** could not be determined.

Finally, the relative and absolute stereochemistries of products **193a**, **193b**, **193d**, **193e**, **193k** and **196c** were determined by single crystal X-ray crystallography using a copper radiation source (Figure 2.5A).



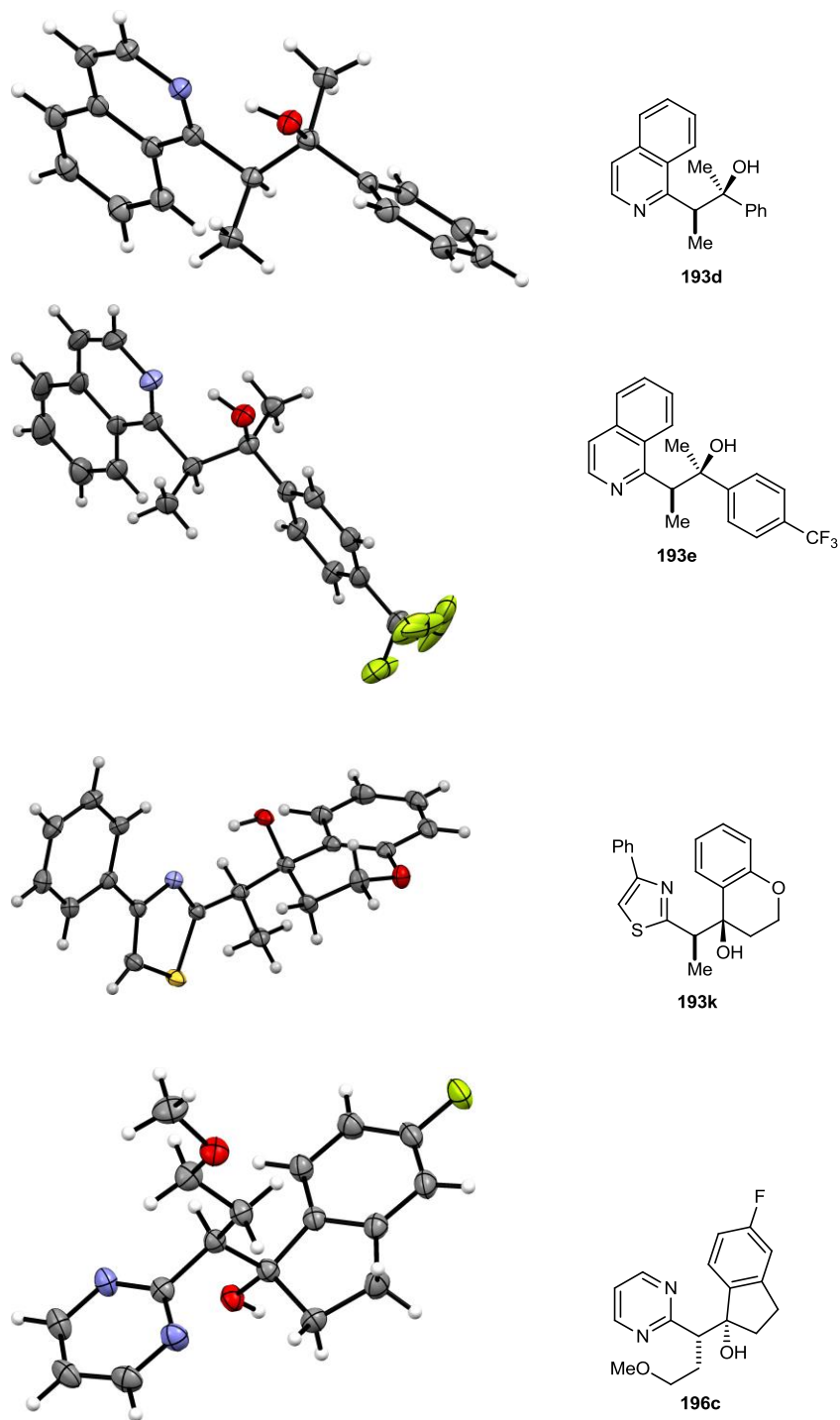


Figure 2.5A: Stereochemical Determination of Reductive Aldol Products

The stereochemistry of **193f** and **193g** were assigned by analogy with **193d** and **193e** (all obtained using ligand **L13**) as illustrated in Figure 2.5B.

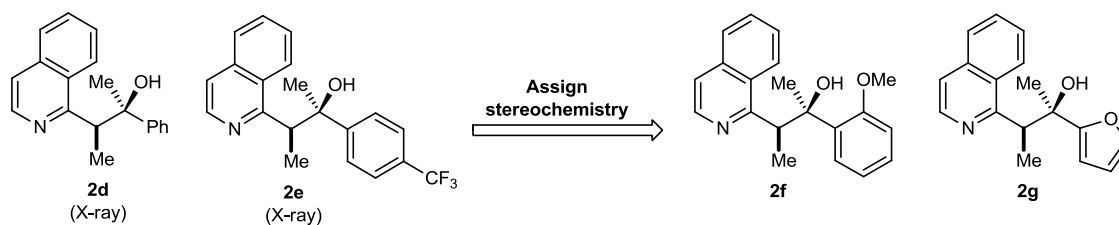


Figure 2.5B: Stereochemical Determination of Reductive Aldol Products

The stereochemistry of **193i**, **193j**, **196a**, and **196b** were assigned by analogy with **196c** (all obtained using ligand **L13**) as illustrated in Figure 2.5C.

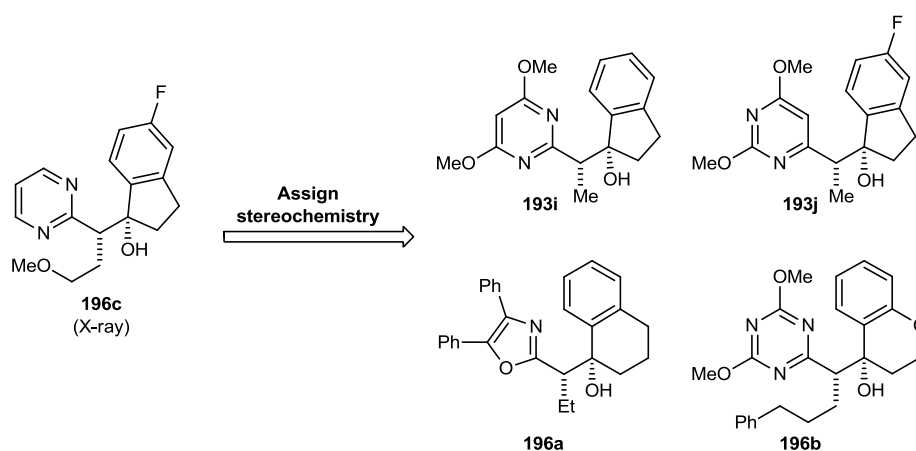


Figure 2.5C: Stereochemical Determination of Reductive Aldol Products

The stereochemistry of **193l** was assigned by analogy with **193k** (both obtained using ligand **L11**) as illustrated in Figure 2.5D.

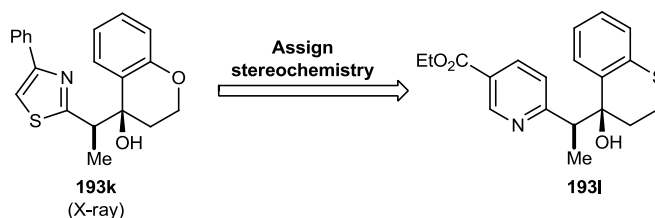


Figure 2.5D: Stereochemical Determination of Reductive Aldol Products

The stereochemistry of **193m** (obtained using ligand **L12**) was assigned by analogy with the product obtained using ligand **L13**, which was the same enantiomer of **193m** but in 2:1 dr and 73% ee (Figure 2.5E).

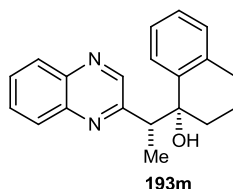


Figure 2.5E: Stereochemical Determination of Reductive Aldol Products

Interestingly, the absolute stereochemistries of isoquinoline-containing products **193d-193g** are opposite to those of quinoline-containing products **193a** and **193b**, even though the same enantiomer of ligand **L13** was employed throughout. In addition, the diastereochemical outcomes of the reactions producing **193i-193m** are different from those resulting in **193a**, **193b**, and **193d-193g**. Assuming that the reactions proceed via Zimmerman–Traxler-type transition states where the larger aryl group of the ketone occupies a pseudoequatorial position,¹⁹¹ Figure 2.6 depicts conformations that are consistent with these observations.

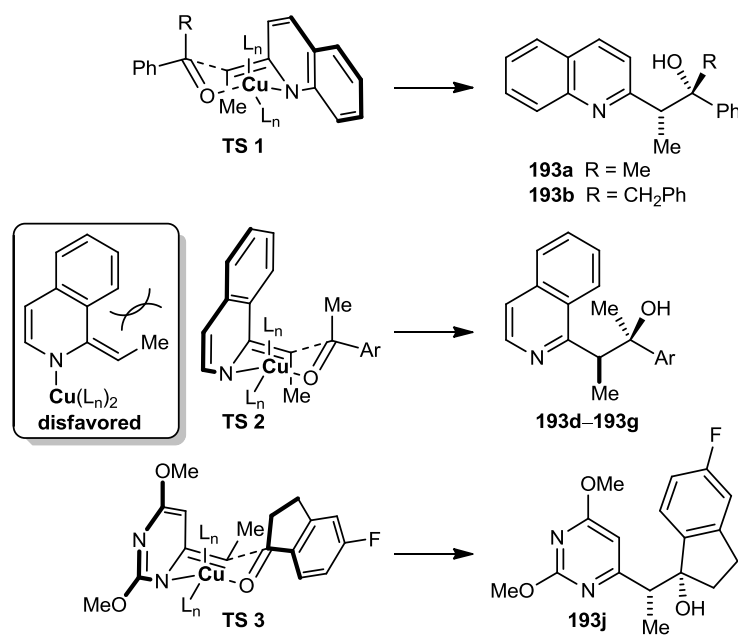
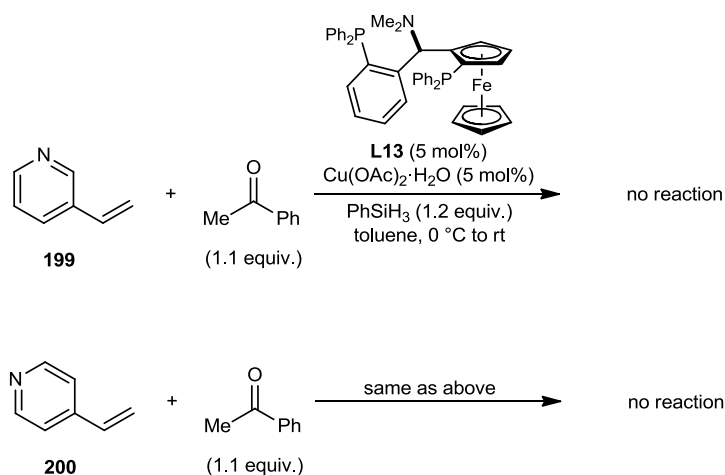


Figure 2.6: Rationalisation of Stereochemical Outcomes

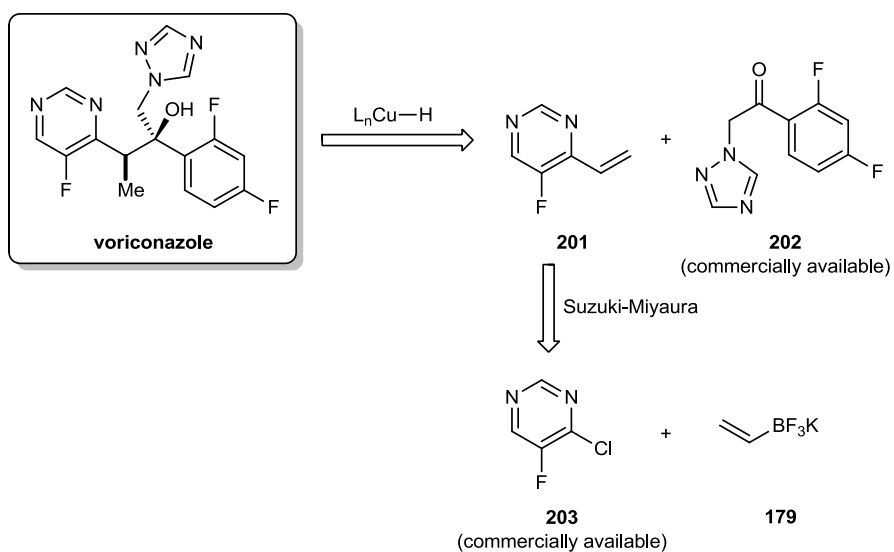
The stereochemical outcomes of the reactions producing **193a**, **193b**, and **193d-193g** are consistent with the participation of *Z*-azaallylcopper species (**TS 1** and **TS 2**), though the reasons for the opposite sense of enantioinduction in **TS 2** compared with **TS 1** are not clear at this time. Furthermore, while the preference for the *Z*-azaallylcopper species in **TS 2** is readily explained by the severe $A_{1,3}$ -strain¹⁹² that would disfavour the corresponding *E*-azaallylcopper species, a similar argument cannot be used to explain the same preference in **TS 1**. For reactions producing **193i-193m**, reaction through the *E*-azaallylcopper species (or *Z*-azaallylcopper species in the case of **193k**) appears to be favoured, as in **TS 3** for the formation of **193j**. The interplay between the steric and/or electronic properties of the alkenylazaarene and ligand, and the resulting effect on the stereochemical outcome, are clearly complex. In addition, while the preceding discussion has been based upon the assumption that chair-like transition states are operative, reaction through boat-like structures cannot be excluded.

Pyridine isomers 3- and 4-vinylpyridine (substrates **199** and **200**, respectively) failed to undergo similar reductive coupling reactions (Equation 2.13). These observations suggest that coordination of copper to the nitrogen atom on the azaarene is necessary for the formation of a 6-membered Zimmerman–Traxler-type transition state.



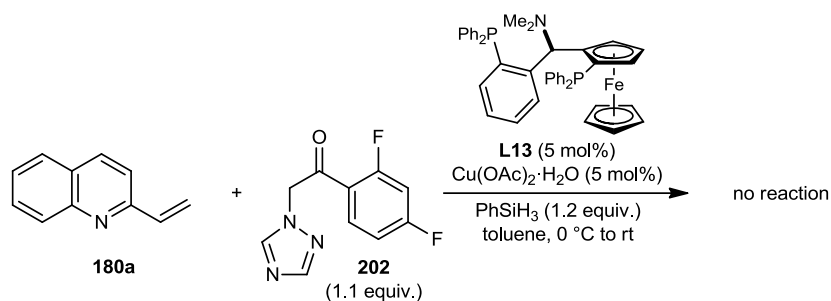
Equation 2.13: Reductive Aldol Coupling of 3- and 4-Vinylpyridine

Potential application of our methodology toward the synthesis of various natural products and pharmaceutical drugs was also surveyed. Preliminary examination prompted Voriconazole as an ideal target candidate. Voriconazole is a triazole antifungal medication that is generally used to treat serious, invasive fungal infections. The drug is marketed by Pfizer.



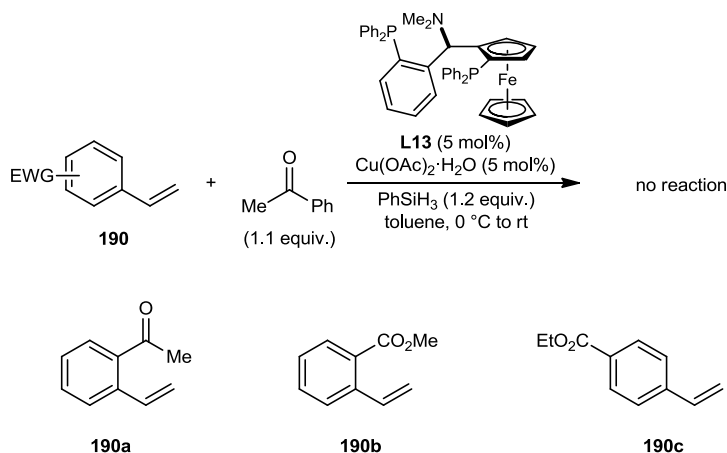
Scheme 2.40: Retrosynthetic Analysis of Voriconazole

Retrosynthetic analysis revealed a short 2-step sequence toward the enantioselective synthesis of Voriconazole (Scheme 2.40). For a quick test of concept, CuH-catalysed reductive coupling of 2-vinylquinoline **180a** with commercially available ketone **202** was attempted (Equation 2.14). Sadly, none of the coupled product was observed. We believe that the nitrogen atoms on the triazole ring of the ketone may be poisoning the system by strongly binding to the copper catalyst. Further experimentation is needed to address this problem and establish a short and enantioselective synthetic route to Voriconazole.



Equation 2.14: Synthesis of Voriconazole Analog

After the completion of this study, we questioned if arenes containing electron-withdrawing substituents could activate an adjacent alkene toward reductive coupling chemistry (Scheme 2.41). Unfortunately, substrates **190a-190c** failed to deliver our desired coupled products.

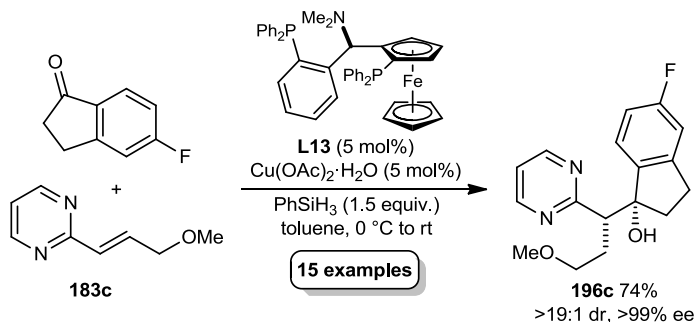


Scheme 2.41: Reductive Aldol Coupling of Electron-Deficient Alkenylarenes with Acetophenone

3. Conclusions

In summary, we have described the first examples of catalytic enantioselective reductive couplings of alkenylazaarenes (Scheme 2.42).¹⁹³ The scope of this process is broad, with eleven different types of azaarenes and a range of acyclic and cyclic ketones having been shown to be effective coupling partners. β -Substitution on the alkene is tolerated, and the

reactions proceed under mild conditions to deliver products in good to high levels of diastereo- and enantioselection.



Scheme 2.42: Reductive Aldol Coupling of Alkenylazaarenes with Ketones

Failure of 3- and 4-vinylpyridine to react with a ketone under our developed set of conditions revealed essential structural requirements of our alkenylazaarene substrates necessary for the production of reductively coupled products.

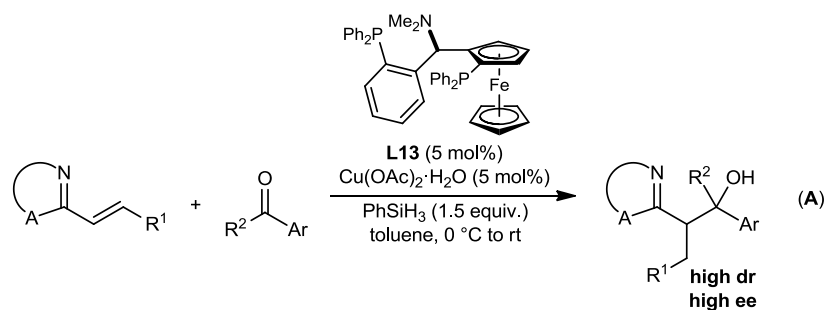
Finally, the synthesis of Voriconazole, an antifungal drug, was attempted. Despite its failure, we believe our developed methodology should be advantageous for its application in the preparation of other novel enantioenriched chiral azaarene-containing building blocks.

4. Future Work

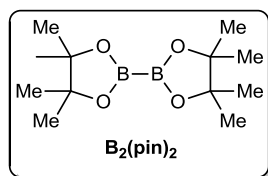
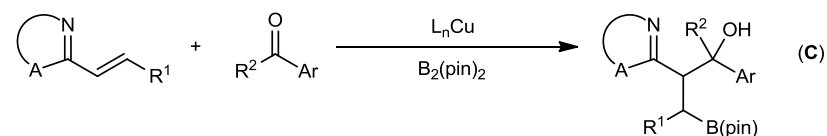
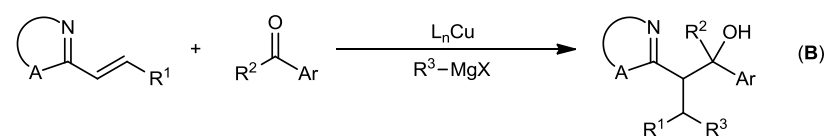
The enantioselective CuH-catalysed reductive aldol coupling chemistry studied in our group opens two obvious avenues for further exploration:

- Changing the nucleophile, resulting in the initial formation of a carbon–carbon or a carbon–heteroatom bond (Scheme 2.43B and 2.43C, respectively) instead of a carbon–hydrogen bond (Scheme 2.43A). The ability to initiate the reaction through the generation of a carbon–carbon or a carbon–boron bond would make the process more divergent by granting access to a variety of chiral compounds starting from a single substrate.

Initial C–H bond formation (this work):



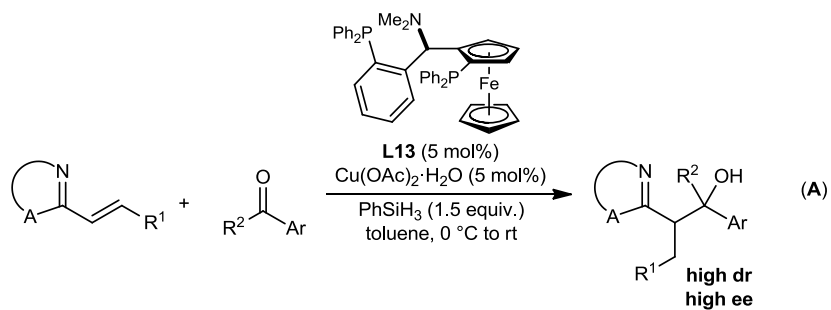
Initial C–C or C–B bond formation (future work):



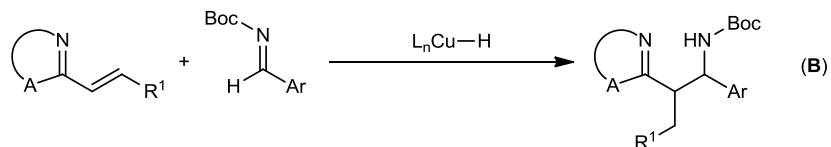
Scheme 2.43: Domino Conjugate Addition/Aldol Coupling of Alkenylazaarenes

- (b) Changing the electrophile, resulting in the trapping of the organocopper intermediate by non-carbonyl functional groups, thereby affording a diverse range of products (Scheme 2.44).

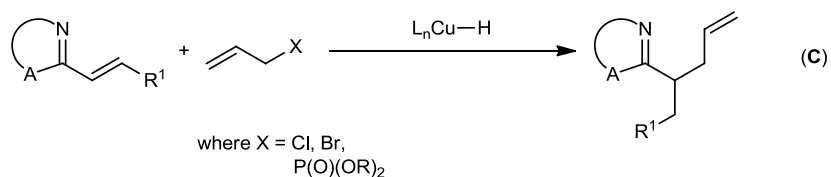
Trapping with ketone (this work):



Trapping with imine (future work):

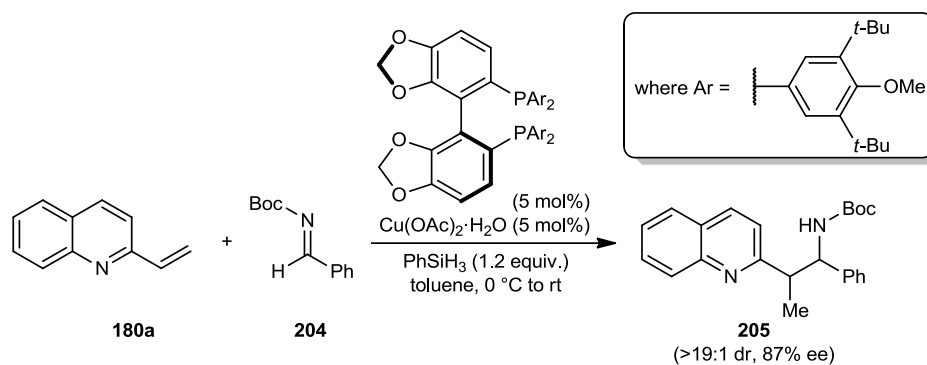


Trapping with allylating agent (future work):



Scheme 2.44: Domino Conjugate Addition/Mannich Reaction or Conjugate Addition/Allylic Substitution Reaction of Alkenylazaarenes

After the successful completion of our reductive aldol chemistry where alkenylazaarenes were coupled with ketones, efforts were directed toward a similar reductive Mannich-type coupling of alkenylazaarenes with imines (Scheme 2.44B). Proof of concept has been established through the enantioselective coupling of 2-vinyquinoline **180a** with imine **204**, affording our Mannich-type product **205** with high diastereo- and enantioselectivity (Equation 2.15).



Equation 2.15: CuH-Catalysed Reductive Mannich-Type Coupling of 2-Vinylquinoline with an Imine

Due to this project being in its early stages of development, product **205** has not yet been isolated and fully characterised. The scope of this process is under investigation by current members of our group and will be reported in due course.

III. Experimental

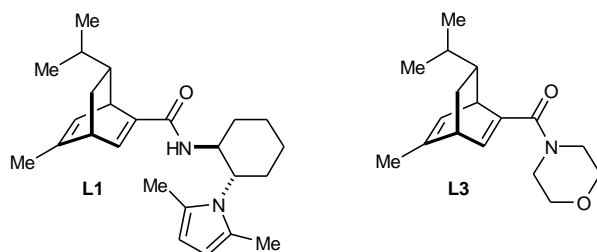
Chapter I: Enantioselective Rhodium-Catalysed Arylation of Electron-Deficient Alkenylarenes

General Information

CH₂Cl₂, MeCN, and THF were dried and purified by passage through activated alumina columns using a solvent purification system from <http://www.glasscontoursolvents.com>. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilen 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.¹⁹⁴ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker AVA500 (500 MHz), a Bruker AVA400 (400 MHz), or a Bruker DPX360 (360 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker AVA500 (125.8 MHz) spectrometer, a Bruker AVA400 (100.6 MHz), or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. ¹⁹F NMR spectra were recorded on a Bruker AVA400 (376 MHz) spectrometer. Chemical shifts (δ) are quoted

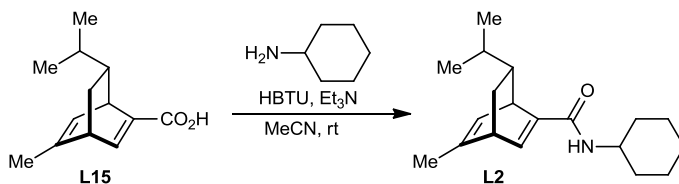
in parts per million (ppm) downfield of CFCl_3 ($\delta = 0$ ppm), using fluorobenzene as internal standard ($\text{C}_6\text{H}_5\text{F}$ at -113.5 ppm). High resolution mass spectra were recorded using electrospray ionization (ES), electron impact (EI), or atmospheric solids analysis probe (ASAP) techniques on a Finnigan MAT 900 XLT spectrometer, a Finnigan MAT 95XP spectrometer, or a Thermofisher LTQ Orbitrap XL spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Chiral HPLC analysis was performed on an Agilent 1100 instrument using 4.6×250 mm columns. Authentic racemic samples of products for chiral HPLC assay determinations were obtained using $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol %) as an achiral precatalyst, using thermal heating. Reactions using microwave heating were carried out in a Biotage microwave synthesizer.

Preparation of Chiral Dienes



Chiral dienes **L1** and **L3** were prepared according to a previously reported procedure.⁴³

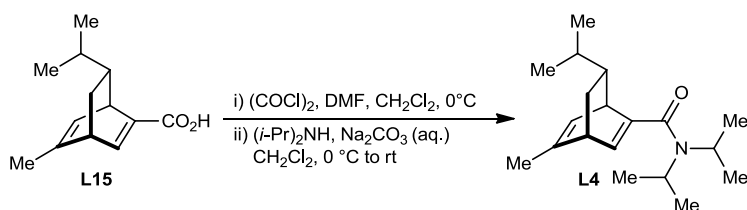
(1*R*,4*R*,7*R*)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid cyclohexylamide (**L2**)



To a solution of carboxylic acid **L15**^{43, 93} (83 mg, 0.40 mmol), HBTU (167 mg, 0.44 mmol), and Et_3N (70 μL , 0.44 mmol) in MeCN (8 mL) at room temperature was added cyclohexylamine (55 μL , 0.48 mmol) in one portion, and the reaction was stirred at room temperature for 1 h. The reaction was diluted with brine (8 mL) and the mixture was

extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 2 M HCl (30 mL), saturated aqueous NaHCO₃ solution (30 mL), and brine (30 mL), and then dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *amide* **L2** (95 mg, 83%) as a colorless solid. m.p. 32-34 °C; $[\alpha]_D^{20} +23.5$ (*c* 1.10, CHCl₃); IR (film) 3312 (NH), 2930, 1628 (C=O), 1528, 1449, 1256, 908, 814 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.76 (1H, dd, *J* = 6.2, 1.8 Hz, =CH), 5.81 (1H, d, *J* = 6.0 Hz, =CH), 5.51 (1H, br d, *J* = 7.2 Hz, NH), 4.02 (1H, dt, *J* = 6.0, 1.9 Hz, =CHCH), 3.86-3.76 (1H, m, NCH), 3.35-3.29 (1H, m, =CHCH), 1.99-1.89 (2H, m), 1.82 (3H, d, *J* = 1.6 Hz, =CCH₃), 1.75-1.66 (2H, m), 1.64-1.55 (2H, m), 1.42-1.34 (2H, m), 1.32-1.03 (5H, m), 1.00 (3H, d, *J* = 6.4 Hz, CH(CH₃)₂), 0.95 (1H, ddd, *J* = 11.5, 4.8, 2.4 Hz, CH), 0.82 (3H, d, *J* = 6.4 Hz, CH(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 165.1 (C), 145.3 (C), 143.9 (C), 137.1 (CH), 124.2 (CH), 48.0 (CH), 47.8 (CH), 43.5 (CH), 40.0 (CH), 33.8 (CH), 33.3 (CH₂), 33.2 (CH₂), 31.8 (CH₂), 25.6 (CH₂), 24.9 (CH₂), 24.9 (CH₂), 21.8 (CH₃), 21.3 (CH₃), 19.0 (CH₃); HRMS (ES) Exact mass calculated for C₁₉H₃₀N₁O₁ [M+H]⁺: 288.2322, found: 288.2325.

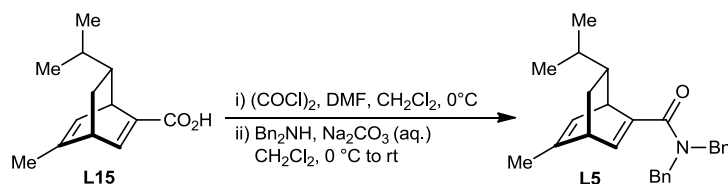
(1*R*,4*R*,7*R*)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid diisopropylamide (L4)



To a solution of carboxylic acid **L15**^{43, 93} (70 mg, 0.34 mmol) and DMF (6 μ L, 0.68 mmol) in CH₂Cl₂ (0.6 mL) at 0 °C was added oxalyl chloride (32 μ L, 0.37 mmol) dropwise over 1 min. The mixture was stirred at 0 °C for 1.5 h (until no more effervescence was observed) to give a solution of the corresponding acid chloride. To a separate mixture of diisopropylamine (50 μ L, 0.35 mmol) in CH₂Cl₂ (1 mL) and saturated aqueous Na₂CO₃ solution (1 mL) at 0 °C was added the solution of the acid chloride dropwise *via* cannula. The mixture was then stirred at room temperature for 20 h. The mixture was partitioned between saturated aqueous NaHCO₃ solution (4 mL) and CH₂Cl₂ (4 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 4 mL).

The combined organic layers were washed with 10% HCl solution (5 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (1% EtOAc/hexane→8% EtOAc/hexane) gave the *diisopropyl amide* **L4** (57 mg, 58%) as a colorless oil. $[\alpha]_D^{20} +28.6$ (*c* 0.41, CHCl₃); IR (film) 2963, 2870, 1609 (C=O), 1439, 1369, 1213, 1159, 1079, 885, 732 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.20 (1H, dd, *J* = 6.1, 1.6 Hz, =CH), 5.77 (1H, d, *J* = 5.8 Hz, =CH), 3.73 (2H, br s, 2 x NCH) 3.58 (1H, dt, *J* = 5.7, 1.8 Hz, =CHCH), 3.25 (1H, app dd, *J* = 5.8, 2.3 Hz, =CHCH), 1.80 (3H, d, *J* = 1.6 Hz, =CCH₃), 1.62 (1H, ddd, *J* = 11.6, 8.9, 2.9 Hz, CH), 1.50-1.32 (12H, m, 4 x CH₃), 1.27-1.11 (2H, m, CH₂), 0.94 (3H, d, *J* = 6.3 Hz, CH₃), 0.89 (1H, ddd, *J* = 11.6, 8.9, 2.9 Hz, CH), 0.79 (3H, d, *J* = 6.3 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 170.7 (C), 146.1 (C), 144.3 (C), 131.2 (CH), 123.5 (CH), 48.1 (CH), 43.1 (CH), 42.7 (CH), 34.0 (CH), 32.1 (CH₂), 21.7 (CH₃), 21.3 (CH₃), 20.9 (2 x CH₃), 20.8 (2 x CH₃), 19.1 (CH₃) (2 x CH next to nitrogen were not observed); HRMS (ES) Exact mass calcd for C₁₉H₃₂N₁O₁ [M+H]⁺: 290.2478, found: 290.2473.

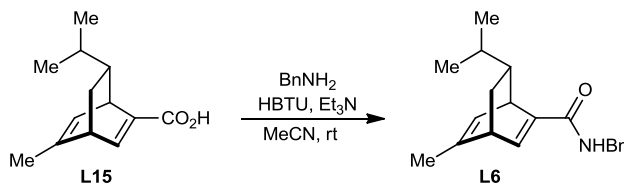
(1R,4R,7R)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid dibenzylamide (L5)



To a solution of carboxylic acid **L15**^{43, 93} (500 mg, 2.42 mmol) and DMF (42 μ L, 0.55 mmol) in CH₂Cl₂ (4.5 mL) at 0 °C was added oxalyl chloride (230 μ L, 2.67 mmol) dropwise over 2 min. The mixture was stirred at 0 °C for 1.5 h (until no more effervescence was observed) to give a solution of the corresponding acid chloride. To a separate mixture of dibenzylamine (423 μ L, 2.20 mmol) in CH₂Cl₂ (5 mL) and saturated aqueous Na₂CO₃ solution (5 mL) at 0 °C was added the solution of the acid chloride dropwise *via* cannula over 1 min. The mixture was then stirred at room temperature for 21 h. The mixture was partitioned between saturated aqueous NaHCO₃ solution (10 mL) and CH₂Cl₂ (10 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with 10% HCl solution (15 mL), dried

(MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (3% EtOAc/hexane) gave the *dibenzyl amide* **L5** (820 mg, 97%) as a colorless oil. $[\alpha]_{\text{D}}^{20} +14.1$ (*c* 0.72, CHCl₃); IR (film) 2958, 2862, 1608 (C=O), 1542, 1426, 1259, 1099, 1017, 892, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.37-7.29 (6H, m, ArH), 7.20-7.18 (4H, m, ArH), 6.50 (1H, dd, *J* = 6.1, 1.6 Hz, =CH), 5.77 (1H, d, *J* = 5.8 Hz, =CH), 4.60-4.41 (4H, m, 2 x NCH₂), 3.83 (1H, dt, *J* = 5.8, 1.8 Hz, =CHCH), 3.28 (1H, app dd, *J* = 5.8, 2.2 Hz, =CHCH), 1.79 (3H, d, *J* = 1.4 Hz, =CCH₃), 1.64 (1H, ddd, *J* = 11.5, 8.9, 2.9 Hz, CH), 1.46-1.40 (1H, m, CH), 1.13-1.01 (1H, m, CH₂), 0.96 (3H, d, *J* = 6.4 Hz, CH₃), 0.95-0.90 (1H, m, CH₂), 0.82 (3H, d, *J* = 6.4 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.2 (C), 144.4 (C), 143.8 (C), 137.2 (2 x C), 135.0 (CH), 128.6 (6 x CH), 127.3 (4 x CH), 123.5 (CH), 48.1 (CH), 43.3 (CH), 42.8 (CH), 33.9 (CH), 32.0 (CH₂), 21.7 (CH₃), 21.3 (CH₃), 19.1 (CH₃) (2 x CH₂ next to nitrogen were not observed); HRMS (ES) Exact mass calcd for C₂₇H₃₂N₁O₁ [M+H]⁺: 386.2478, found: 386.2471.

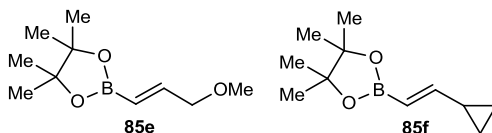
(1R,4R,7R)-7-Isopropyl-5-methyl-bicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid benzylamide (L6)



To a solution of carboxylic acid **L15**^{43, 93} (83 mg, 0.40 mmol), HBTU (167 mg, 0.44 mmol), and Et₃N (70 μ L, 0.44 mmol) in MeCN (8 mL) at room temperature was added benzylamine (53 μ L, 0.48 mmol) in one portion, and the reaction was stirred at room temperature for 1 h. The reaction was diluted with brine (8 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with 2 M HCl (30 mL), saturated aqueous NaHCO₃ solution (30 mL), and brine (30 mL), and then dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *amide* **L6** (81 mg, 68%) as a white solid. *R*_f = 0.40 (20% EtOAc/hexane); m.p. 112-114 °C; $[\alpha]_{\text{D}}^{20} +25.4$ (*c* 1.10, CHCl₃); IR (film) 3314 (NH), 2949, 2864, 1631 (C=O), 1535, 1282, 1028, 802, 678 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.21 (5H, m, ArH), 6.79 (1H, dd, *J* = 6.2, 1.4 Hz, =CH), 5.90 (1H,

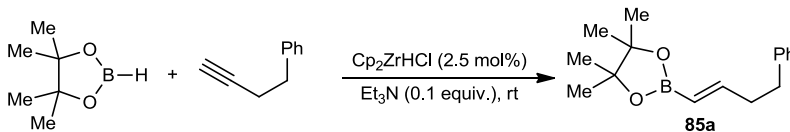
br s, NH), 5.77 (1H, d, $J = 5.7$ Hz, =CH), 4.51-4.41 (2H, m, NCH₂), 4.07-3.99 (1H, m, =CHCH), 3.34-3.26 (1H, m, =CHCH), 1.78 (3H, br s, =CCH₃), 1.54 (1H, ddd, $J = 11.5$, 9.1, 2.8 Hz, CH), 1.30-1.17 (1H, m, CH₂), 1.11-1.01 (1H, m, CH₂), 0.97 (3H, d, $J = 6.4$ Hz, CH(CH₃)₂), 0.92 (1H, ddd, $J = 11.5$, 5.6, 2.5 Hz, CH), 0.79 (3H, d, $J = 6.4$ Hz, CH(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 165.8 (C), 144.8 (C), 143.8 (C), 138.5 (C), 138.0 (CH), 128.7 (2 x CH), 127.9 (2 x CH), 127.4 (CH), 124.1 (CH), 47.8 (CH), 43.6 (CH₂), 43.6 (CH), 40.0 (CH), 33.8 (CH), 31.7 (CH₂), 21.8 (CH₃), 21.4 (CH₃), 19.0 (CH₃); HRMS (ES) Exact mass calculated for C₂₀H₂₆N₁O₁ [M+H]⁺: 296.2009, found: 296.2012.

Preparation of Alkenylboronic Esters



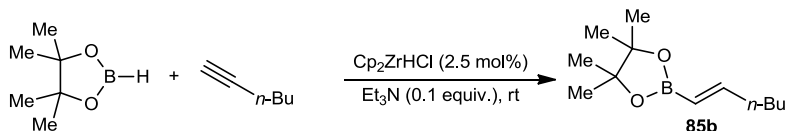
Alkenylboronic esters **85e** and **85f** are commercially available from Sigma-Aldrich.

4,4,5,5-Tetramethyl-2-[(*E*)-4-phenylbut-1-enyl]-[1,3,2]dioxaborolane (**85a**)



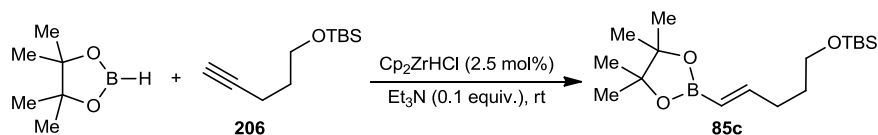
To a mixture of 4-phenylbut-1-yne (5.62 mL, 40.0 mmol), Cp₂ZrHCl (292 mg, 1.00 mmol), and Et₃N (0.56 mL, 4.00 mmol) at room temperature was added pinacolborane (5.80 mL, 40.0 mmol) over 2 min, and the mixture was stirred for 16 h. The reaction was quenched carefully with H₂O (75 mL) and after effervescence had ceased, the mixture was extracted with Et₂O (2 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *alkenylboronic ester* **85a** (7.86 g, 76%) as a colorless oil that displayed spectroscopic data consistent with those observed previously.¹⁹⁵

4,4,5,5-Tetramethyl-2-[(*E*)-hex-1-enyl]-[1,3,2]dioxaborolane (**85b**)



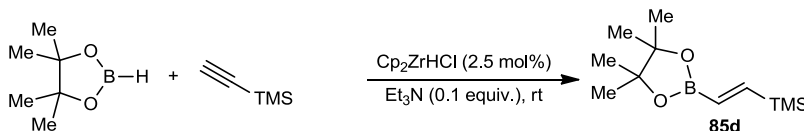
To a mixture of 1-hexyne (4.60 mL, 40.0 mmol), Cp_2ZrHCl (292 mg, 1.00 mmol), and Et_3N (0.56 mL, 4.00 mmol) at room temperature was added pinacolborane (5.80 mL, 40.0 mmol) over 2 min, and the mixture was stirred for 16 h. The reaction was quenched carefully with H_2O (75 mL) and after effervescence had ceased, the mixture was extracted with Et_2O (2 x 100 mL). The combined organic extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc /hexane) gave the *alkenylboronic ester* **85b** (6.75 g, 80%) as a colorless oil that displayed spectroscopic data consistent with those observed previously.⁷⁵

4,4,5,5-Tetramethyl-2-[(*E*)-5-*tert*-butyldimethylsilyloxypent-1-enyl]-[1,3,2]dioxaborolane (85c**)**



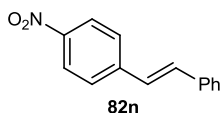
To a mixture of alkyne **206** (5.95 mL, 30.0 mmol), Cp_2ZrHCl (219 mg, 0.75 mmol), and Et_3N (0.42 mL, 3.00 mmol) at room temperature was added pinacolborane (4.35 mL, 30.0 mmol) over 2 min, and the mixture was stirred for 16 h. The reaction was quenched carefully with H_2O (75 mL) and after effervescence had ceased, the mixture was extracted with Et_2O (2 x 100 mL). The combined organic extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc /hexane) gave the *alkenylboronic ester* **85c** (8.01 g, 82%) as a colorless oil that displayed spectroscopic data consistent with those observed previously.⁷⁵

4,4,5,5-Tetramethyl-2-[(*E*)-trimethylsilylethenyl]-[1,3,2]dioxaborolane (85d**)**



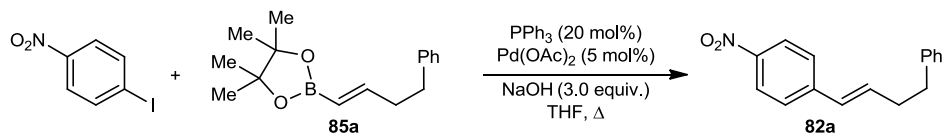
To a mixture of ethynyl(trimethyl)silane (2.83 mL, 20.0 mmol), Cp_2ZrHCl (146 mg, 0.50 mmol), and Et_3N (0.28 mL, 2.00 mmol) at room temperature was added pinacolborane (2.90 mL, 20.0 mmol) over 2 min, and the mixture was stirred for 16 h. The reaction was quenched carefully with H_2O (30 mL) and after effervescence had ceased, the mixture was extracted with Et_2O (2 x 50 mL). The combined organic extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (30% CH_2Cl_2 /hexane) gave the *alkenylboronic ester* **85d** (716 mg, 16%) as a colorless oil that displayed spectroscopic data consistent with those observed previously.¹⁹⁶

Preparation of Alkenylarenes



Alkenylarene **82n** is commercially available from TCI.

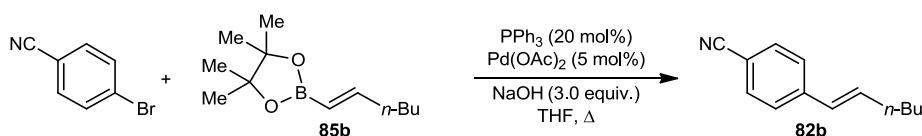
1-Nitro-4-[(*E*)-4-phenylbut-1-enyl]benzene (**82a**)



A solution of 1-iodo-4-nitrobenzene (1.49 g, 6.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.70 g, 6.60 mmol), $\text{Pd}(\text{OAc})_2$ (67 mg, 0.30 mmol), PPh_3 (315 mg, 1.20 mmol), and NaOH (720 mg, 18.0 mmol) in THF (60 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et_2O (100 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl solution (80 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH_2Cl_2 /hexane→40% CH_2Cl_2 /hexane) gave the *alkenylarene* **82a** (1.11 g, 73%) as a yellow solid. m.p. 68-70 °C; IR (film) 3028, 2937, 1595, 1514 (N-O),

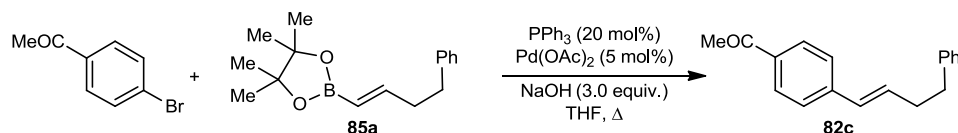
1340 (N-O), 1107, 968, 864, 744, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.18 (2H, d, J = 8.9 Hz, ArH), 7.46 (2H, d, J = 8.9 Hz, ArH), 7.41-7.35 (2H, m, ArH), 7.32-7.26 (3H, m, ArH), 6.53-6.49 (2H, m, CH=CH), 2.93-2.86 (2H, m, CH_2Ph), 2.70-2.61 (2H, m, =CHCH $_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 146.3 (C), 144.0 (C), 141.0 (C), 135.1 (CH), 128.5 (CH), 128.30 (2 x CH), 128.27 (2 x CH), 126.2 (2 x CH), 125.9 (CH), 123.7 (2 x CH), 35.2 (CH_2), 34.8 (CH_2); HRMS (EI) Exact mass calcd for $\text{C}_{16}\text{H}_{15}\text{N}_1\text{O}_2$ $[\text{M}]^+$: 253.1097, found: 253.1096.

4-[(*E*)-hex-1-enyl]benzonitrile (**82b**)



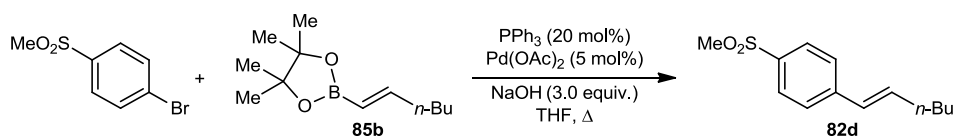
A solution of 4-bromobenzonitrile (910 mg, 5.00 mmol), alkenylboronic ester **85b**⁷⁵ (1.16 g, 5.50 mmol), $\text{Pd}(\text{OAc})_2$ (56 mg, 0.25 mmol), PPh_3 (262 mg, 1.00 mmol), and NaOH (600 mg, 15.0 mmol) in dry THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et_2O (100 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl solution (80 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH_2Cl_2 /hexane \rightarrow 40% CH_2Cl_2 /hexane) gave the *alkenylarene* **82b** (830 mg, 90%) as a pale yellow oil. IR (film) 2958, 2929, 2871, 2225 ($\text{C}\equiv\text{N}$), 1649, 1604, 1466, 1174, 968, 858 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.57 (2H, d, J = 8.3 Hz, ArH), 7.41 (2H, d, J = 8.3 Hz, ArH), 6.41-6.36 (2H, m, CH=CH), 2.30-2.21 (2H, m, =CHCH $_2$), 1.52-1.33 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.94 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 142.4 (C), 135.6 (CH), 132.3 (2 x CH), 128.4 (CH), 126.3 (2 x CH), 119.2 (C), 109.9 (C), 32.8 (CH_2), 31.1 (CH_2), 22.2 (CH_2), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{17}\text{H}_{28}\text{N}_1\text{O}_3\text{Si}_1$ $[\text{M}+\text{H}]^+$: 186.1277, found: 186.1280.

1-{4-[(*E*)-4-Phenylbut-1-enyl]phenyl}ethan-1-one (**82c**)



A solution of 1-acetyl-4-bromobenzene (796 mg, 4.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.14 g, 4.40 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), PPh₃ (210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in dry THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82c** (946 mg, 95%) as an off-white solid. m.p. 60-62 °C; IR (film) 3030, 2931, 1676 (C=O), 1454, 1360, 1271, 970, 856, 748, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.95 (2H, d, *J* = 8.4 Hz, ArH), 7.45 (2H, d, *J* = 8.4 Hz, ArH), 7.42-7.34 (2H, m, ArH), 7.33-7.26 (3H, m, ArH), 6.56-6.41 (2H, m, ArCH=CH), 2.92-2.83 (2H, m, CH₂Ph), 2.67-2.57 (5H, m, CH₂CH₂Ph and CCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 197.1 (C), 142.1 (C), 141.2 (C), 135.3 (C), 132.9 (CH), 129.4 (CH), 128.5 (2 x CH), 128.2 (2 x CH), 128.2 (2 x CH), 125.8 (2 x CH), 35.3 (CH₂), 34.7 (CH₂), 26.3 (CH₃); HRMS (APCI) Exact mass calcd for C₁₈H₁₉O₁ [M+H]⁺: 251.1430, found: 251.1432.

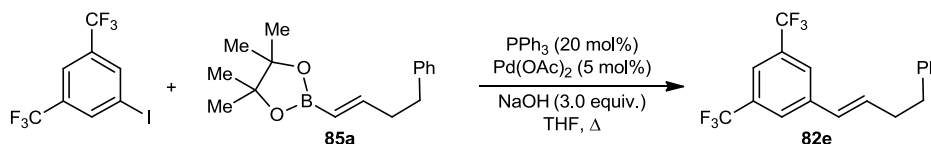
1-[(*E*)-Hex-1-enyl]-4-methanesulfonylbenzene (**82d**)



A solution of 1-bromo-4-(methylsulfonyl)benzene (940 mg, 4.00 mmol), alkenylboronic ester **85b**⁷⁵ (925 mg, 4.40 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), PPh₃ (210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in dry THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by

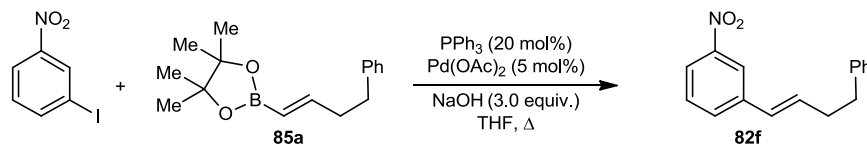
column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82d** (887 mg, 93%) as a yellow solid. m.p. 40-42 °C; IR (film) 2956, 2925, 2856, 1593 (C=C), 1406, 1304, 1149, 968, 858, 764 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.74 (2H, d, *J* = 8.5 Hz, ArH), 7.38 (2H, d, *J* = 8.5 Hz, ArH), 6.36-6.25 (2H, m, CH=CH), 2.93 (2H, s, SO₂CH₃), 2.20-2.09 (2H, m, =CHCH₂), 1.45-1.20 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 142.8 (C), 137.9 (C), 135.2 (CH), 127.8 (CH), 127.2 (2 x CH), 126.1 (2 x CH), 44.0 (CH₃), 32.3 (CH₂), 30.7 (CH₂), 21.8 (CH₂), 13.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₃H₁₉O₂S₁ [M+H]⁺: 239.1100, found: 239.1097.

1-[(*E*)-4-Phenylbut-1-enyl]-3,5-bis(trifluoromethyl)benzene (**82e**)



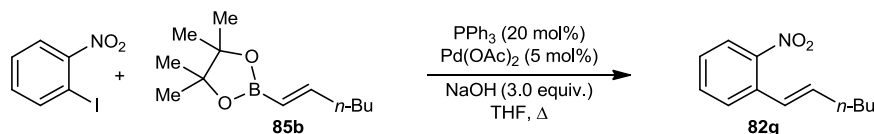
A solution of 3,5-bis(trifluoromethyl)iodobenzene (0.89 mL, 5.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.42 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol), and NaOH (600 mg, 15.0 mmol) in dry THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) gave the *alkenylarene* **82e** (1.60 g, 93%) as a colourless oil. IR (film) 3030, 2929, 1604 (C=C), 1454, 1381, 1282, 1134, 966, 895, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.81 (2H, s, ArH), 7.79 (1H, s, ArH), 7.45-7.38 (2H, m, ArH), 7.35-7.28 (3H, m, ArH), 6.54-6.49 (2H, m, CH=CH), 2.96-2.88 (2H, m, =CHCH₂), 2.72-2.63 (2H, m, CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 141.2 (C), 139.7 (C), 134.3 (CH), 131.8 (2 x C, q, *J* = 33.1 Hz, CCF₃), 128.5 (2 x CH), 128.4 (2 x CH), 128.1 (CH), 126.1 (CH), 125.8 (2 x CH, d, *J* = 2.7 Hz, ArC), 123.4 (2 x C, q, *J* = 272.6 Hz, CF₃), 120.3 (CH, td, *J* = 7.7, 3.8 Hz, ArC), 35.4 (CH₂), 34.8 (CH₂); HRMS (EI) Exact mass calcd for C₁₆H₁₅N₁O₂ [M]⁺: 344.0994, found: 344.0995.

1-Nitro-3-[(*E*)-4-phenylbut-1-enyl]benzene (**82f**)



A solution of 1-iodo-3-nitrobenzene (996 mg, 4.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.14 g, 4.40 mmol), $\text{Pd}(\text{OAc})_2$ (45 mg, 0.20 mmol), PPh_3 (210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in dry THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et_2O (50 mL) and H_2O (30 mL). The aqueous layer was separated and extracted with Et_2O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl solution (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% $\text{CH}_2\text{Cl}_2/\text{hexane}$ →40% $\text{CH}_2\text{Cl}_2/\text{hexane}$) gave the *alkenylarene* **82f** (957 mg, 95%) as a dark yellow oil. IR (film) 3028, 2925, 2856, 1529 (N-O), 1350 (N-O), 1076, 964, 820, 733, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.19 (1H, s, ArH), 8.10-8.02 (1H, m, ArH), 7.62 (1H, d, $J = 7.7$ Hz, ArH), 7.46 (1H, t, $J = 7.9$ Hz, ArH), 7.33 (2H, t, $J = 7.6$ Hz, ArH), 7.29-7.20 (3H, m, ArH), 6.51-6.38 (2H, m, ArCH=CH), 2.89-2.80 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$), 2.65-2.55 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 148.6 (C), 141.2 (C), 139.4 (C), 133.4 (CH), 131.8 (CH), 129.3 (CH), 128.4 (2 x CH), 128.4 (2 x CH), 128.3 (CH), 126.0 (CH), 121.5 (CH), 120.5 (CH), 35.5 (CH), 34.7 (CH_2); HRMS (EI) Exact mass calcd for $\text{C}_{16}\text{H}_{15}\text{N}_1\text{O}_2$ $[\text{M}]^+$: 253.1097, found: 253.1095.

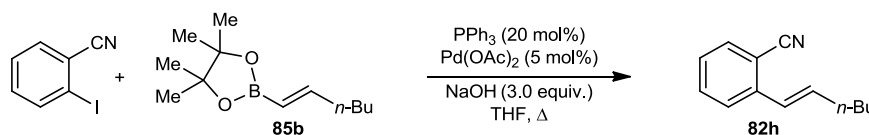
1-[(*E*)-Hex-1-enyl]-2-nitrobenzene (**82g**)



A solution of 1-iodo-2-nitrobenzene (747 mg, 3.00 mmol), alkenylboronic ester **85b**⁷⁵ (693 mg, 3.30 mmol), $\text{Pd}(\text{OAc})_2$ (34 mg, 0.15 mmol), PPh_3 (157 mg, 0.60 mmol), and NaOH (360 mg, 9.0 mmol) in dry THF (30 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et_2O (50 mL) and H_2O

(30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 25 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (40 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82g** (575 mg, 93%) as a yellow oil. IR (film) 2929, 2858, 1606, 1522 (N-O), 1466, 1346 (N-O), 964, 860, 783, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.84 (1H, dd, *J* = 8.2, 1.1 Hz, ArH), 7.57 (1H, dd, *J* = 7.9, 1.1 Hz, ArH), 7.50 (1H, t, *J* = 7.6 Hz, ArH), 7.35-7.28 (1H, m, ArH), 6.82 (1H, d, *J* = 15.7 Hz, ArCH=), 6.23 (1H, td, *J* = 15.6, 6.9 Hz, ArCH=CH), 2.56 (2H, ddd, *J* = 8.3, 7.3, 1.4 Hz, =CHCH₂), 1.59-1.32 (4H, m, CH₂CH₂CH₃), 0.93 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 147.5 (C), 136.8 (CH), 133.2 (C), 128.2 (CH), 127.2 (CH), 124.7 (CH), 124.2 (CH), 32.8 (CH₂), 31.0 (CH₂), 22.1 (CH₂), 13.8 (CH₃); HRMS (EI) Exact mass calcd for C₁₂H₁₅N₁O₂ [M]⁺: 205.1097, found: 205.1095.

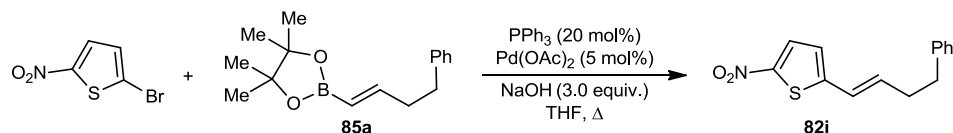
2-[(*E*)-Hex-1-enyl]benzonitrile (**82h**)



A solution of 2-iodobenzonitrile (687 mg, 3.00 mmol), alkenylboronic ester **85b**⁷⁵ (693 mg, 3.30 mmol), Pd(OAc)₂ (34 mg, 0.15 mmol), PPh₃ (157 mg, 0.60 mmol), and NaOH (360 mg, 9.0 mmol) in dry THF (30 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 25 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (40 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82h** (519 mg, 93%) as a yellow oil. IR (film) 2958, 2929, 2871, 2224 (C≡N), 1649, 1597, 1477, 1290, 966, 758 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.61 (2H, t, *J* = 8.5 Hz, ArH), 7.51 (1H, t, *J* = 7.3 Hz, ArH), 7.30-7.24 (1H, m, ArH), 6.75 (1H, d, *J* = 15.7 Hz, ArCH=), 6.45 (1H, td, *J* = 15.6, 7.0 Hz, ArCH=CH), 2.30 (2H, dt, *J* = 8.3, 1.7 Hz, =CHCH₂), 1.49-1.34 (4H, m, CH₂CH₂CH₃), 0.94 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR

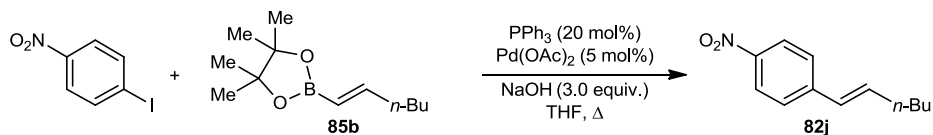
(125.8 MHz, CDCl₃) δ 141.2 (C), 136.9 (CH), 132.9 (CH), 132.7 (CH), 126.9 (CH), 125.8 (CH), 125.3 (CH), 118.2 (C), 110.4 (C), 33.0 (CH₂), 31.2 (CH₂), 22.3 (CH₂), 14.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₃H₁₉N₂ [M+NH₄]⁺: 203.1543, found: 203.1544.

2-Nitro-5-[(*E*)-4-phenylbut-1-en-1-yl]thiophene (**82i**)



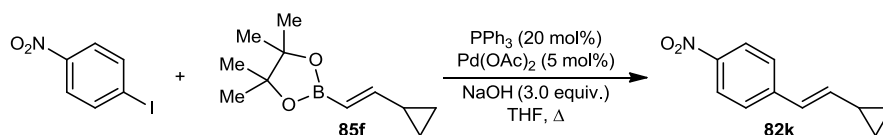
A solution of 2-bromo-5-nitrothiophene (832 mg, 4.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.14 g, 4.40 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), PPh₃ (210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in dry THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *alkenylarene* **82i** (417 mg, 40%) as a red solid. m.p. 64-66 °C; IR (film) 3026, 2933, 1525 (N-O), 1489, 1433, 1329 (N-O), 1032, 960, 806, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.79 (1H, d, *J* = 4.2 Hz, ArH), 7.36-7.29 (2H, m, ArH), 7.27-7.18 (3H, m, ArH), 6.81 (1H, d, *J* = 4.2 Hz, ArH), 6.47 (1H, d, *J* = 15.8 Hz, ArCH=), 6.43-6.34 (1H, m, ArCH=CH), 2.82 (2H, t, *J* = 7.7 Hz, CH₂CH₂Ph), 2.62-2.53 (2H, m, CH₂CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 150.4 (C), 140.8 (C), 136.2 (CH), 129.4 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 126.2 (CH), 123.5 (CH), 122.8 (CH), 35.0 (CH₂), 34.7 (CH₂) (1 C next to sulfur was not observed); HRMS (EI) Exact mass calcd for C₁₄H₁₃N₁O₂S₁ [M]⁺: 259.0662, found: 259.0665.

1-[(*E*)-Hex-1-enyl]-4-nitrobenzene (**82j**)



A solution of 1-iodo-4-nitrobenzene (1.25 g, 5.00 mmol), alkenylboronic ester **85b**⁷⁵ (1.16 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol), and NaOH (600 mg, 15.0 mmol) in dry THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82j** (906 mg, 88%) as a yellow oil. IR (film) 2929, 2858, 1649, 1597, 1518 (N-O), 1346 (N-O), 1109, 970, 862, 744 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.08 (2H, d, *J* = 8.9 Hz, ArH), 7.38 (2H, d, *J* = 8.9 Hz, ArH), 6.41-6.34 (2H, m, CH=CH), 2.26-2.15 (2H, m, =CHCH₂), 1.50-1.29 (4H, m, CH₂CH₂CH₃), 0.91 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 146.1 (C), 144.2 (C), 136.4 (CH), 127.8 (CH), 126.0 (2 x CH), 123.6 (2 x CH), 32.7 (CH₂), 30.9 (CH₂), 22.1 (CH₂), 13.7 (CH₃); HRMS (EI) Exact mass calcd for C₁₂H₁₅N₁O₂ [M]⁺: 205.1097, found: 205.1096.

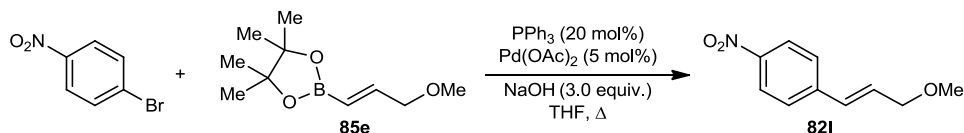
1-[(*E*)-2-Cyclopropylvinyl]-4-nitrobenzene (**82k**)



A solution of 1-iodo-4-nitrobenzene (996 mg, 4.00 mmol), alkenylboronic ester **85f** (854 mg, 4.40 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), PPh₃ (210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82k** (717 mg, 95%) as a yellow solid. m.p. 64-66 °C; IR (film) 3014, 1649, 1593, 1508 (N-O), 1342 (N-O), 1111, 1049, 949, 858, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.15-8.07 (2H, m, ArH), 7.41-7.34 (2H, m, ArH), 6.50 (1H, d, *J* = 15.7 Hz, ArCH=), 5.90 (1H, dd,

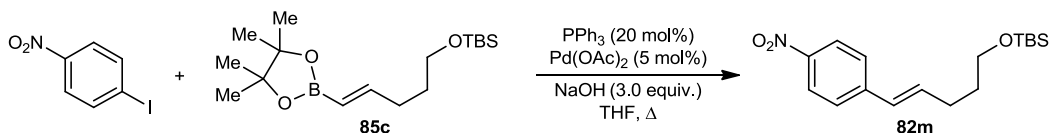
$J = 15.7, 9.3$ Hz, ArCH=CH), 1.69-1.54 (1H, m, =CHCH), 0.98-0.83 (2H, m, CH₂CH₂), 0.65-0.52 (2H, m, CH₂CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 146.0 (C), 144.2 (C), 140.7 (CH), 125.7 (2 x CH), 125.4 (CH), 123.9 (2 x CH), 15.0 (CH), 7.9 (2 x CH₂); HRMS (EI) Exact mass calcd for C₁₁H₁₁N₁O₂ [M]⁺: 189.0784, found: 189.0787.

1-[(*E*)-3-Methoxypropenyl]-4-nitrobenzene (**82l**)



A solution of 1-iodo-4-nitrobenzene (1.01 g, 5.00 mmol), alkenylboronic ester **85e** (1.09 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol), and NaOH (600 mg, 15.0 mmol) in THF (50 mL) was heated to reflux for 5 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *alkenylarene* **82l** (857 mg, 89%) as a cream solid. m.p. 34-36 °C; IR (film) 2930, 1594, 1515, (N-O), 1341 (N-O), 1188, 1120, 1077, 976, 957, 860 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.11-8.04 (2H, m, ArH), 7.48-7.38 (2H, m, ArH), 6.61 (1H, d, $J = 16.0$ Hz, ArCH=), 6.39 (1H, dt, $J = 16.0, 5.3$ Hz, ArCH=CH), 4.07 (2H, dd, $J = 5.4, 1.7$ Hz, CH₂OCH₃), 3.36 (3H, s, OCH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 146.6 (C), 143.0 (C), 131.1 (CH), 129.0 (CH), 126.6 (2 x CH), 123.6 (2 x CH), 72.1 (CH₂), 58.1 (CH₃); m/z (EI) 193 ([M]⁺, 44), 147 (43), 115 (100).

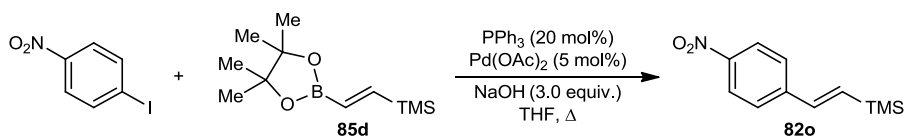
1-[(*E*)-5-*tert*-Butyldimethylsilyloxy-pent-1-enyl]-4-nitrobenzene (**82m**)



A solution of 1-iodo-4-nitrobenzene (4.98 g, 20.0 mmol), alkenylboronic ester **85c**⁷⁵ (7.18 g, 22.0 mmol), Pd(OAc)₂ (225 mg, 1.00 mmol), PPh₃ (1.05 g, 4.00 mmol), and NaOH (2.40 g, 60.0 mmol) in THF (200 mL) was heated to reflux for 16 h. The mixture

was cooled to room temperature, and partitioned between Et₂O (150 mL) and H₂O (100 mL). The aqueous layer was separated and extracted with Et₂O (2 x 150 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (200 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *alkenylarene* **82m** (4.91 g, 76%) as a yellow oil. IR (film) 2931, 1651, 1597, 1518 (N-O), 1344 (N-O), 1255, 1107, 968, 839, 742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.08-8.02 (2H, m, ArH), 7.39-7.33 (2H, m, ArH), 6.45-6.34 (2H, m, CH=CH), 3.63 (2H, t, *J* = 6.2 Hz, CH₂O), 2.34-2.24 (2H, m, =CHCH₂), 1.72-1.62 (2H, m, =CHCH₂CH₂), 0.87 (9H, s, C(CH₃)₃), 0.02 (6H, s, Si(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 146.1 (C), 144.1 (C), 135.8 (CH), 128.1 (CH), 126.0 (2 x CH), 123.6 (2 x CH), 62.0 (CH₂), 31.8 (CH₂), 29.4 (CH₂), 25.7 (3 x CH₃), 18.0 (C), -5.6 (2 x CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₈N₁O₃Si₁ [M+H]⁺: 322.1833, found: 322.1838.

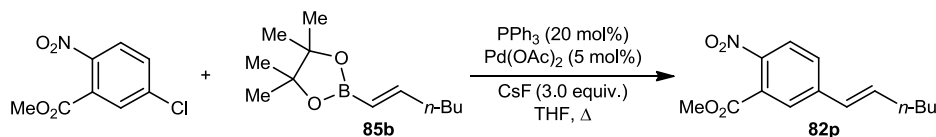
Trimethyl[(*E*)-2-(4-nitrophenyl)vinyl]silane (**82o**)



A solution of 1-iodo-4-nitrobenzene (747 mg, 3.00 mmol), alkenylboronic ester **85d**¹⁹⁶ (679 mg, 3.00 mmol), Pd(OAc)₂ (34 mg, 0.15 mmol), PPh₃ (157 mg, 0.60 mmol), and NaOH (360 mg, 9.00 mmol) in THF (30 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (40 mL) and H₂O (25 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (40 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82o** (523 mg, 79%) as a yellow solid. m.p. 37-39 °C; IR (film) 2956, 1591, 1521 (N-O), 1341 (N-O), 1240, 1109, 993, 861, 839, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.24-8.18 (2H, m, ArH), 7.61-7.53 (2H, m, ArH), 6.95 (1H, d, *J* = 19.1 Hz, ArCH=), 6.74 (1H, d, *J* = 19.1 Hz, ArCH=CH), 0.21 (9H, s, Si(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 147.1

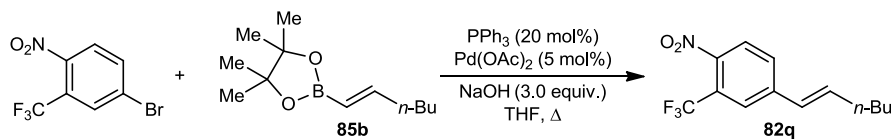
(C), 144.4 (C), 141.2 (CH), 136.1 (CH), 126.8 (2 x CH), 123.9 (2 x CH), -1.5 (3 x CH₃); *m/z* (EI) 221 ([M]⁺, 10), 206 (100), 147 (91).

5-[(*E*)-Hex-1-enyl]-2-nitrobenzoic acid methyl ester (**82p**)



A solution of methyl 5-chloro-2-nitrobenzoate (1.08 g, 5.00 mmol), alkenylboronic ester **85b**⁷⁵ (1.16 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol), and CsF (2.28 g, 15.0 mmol) in THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82p** (407 mg, 31%) as a yellow oil. IR (film) 2956, 1739 (C=O), 1585, 1525 (N-O), 1437, 1344 (N-O), 1259, 1209, 1068, 845 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.86 (1H, d, *J* = 8.5 Hz, ArH), 7.56 (1H, d, *J* = 1.9 Hz, ArH), 7.46 (1H, dd, *J* = 8.5, 1.9 Hz, ArH), 6.48-6.33 (2H, m, CH=CH), 3.89 (3H, s, OCH₃), 2.25-2.21 (2H, m, =CHCH₂), 1.50-1.40 (2H, m, CH₂CH₂CH₃), 1.39-1.29 (2H, m, CH₂CH₃), 0.90 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 166.3 (C), 145.3 (C), 143.3 (C), 137.4 (CH), 128.6 (C), 128.0 (CH), 127.0 (CH), 126.3 (CH), 124.4 (CH), 53.0 (CH₃), 32.7 (CH₂), 30.8 (CH₂), 22.1 (CH₂), 13.7 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₄H₁₇N₁O₄ [M]⁻: 263.1163, found: 263.1156.

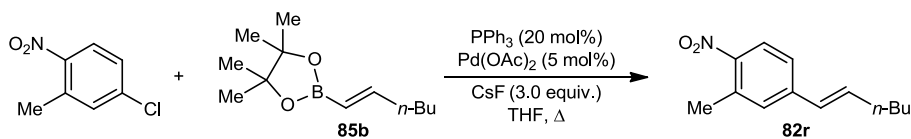
4-[(*E*)-Hex-1-enyl]-1-nitro-2-trifluoromethylbenzene (**82q**)



A solution of 4-bromo-1-nitro-2-(trifluoromethyl)benzene (1.08 g, 4.00 mmol), alkenylboronic ester **85b**⁷⁵ (925 mg, 4.40 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), PPh₃

(210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) gave the *alkenylarene* **82q** (640 mg, 59%) as a yellow oil. IR (film) 2931, 1651, 1591, 1537 (N-O), 1354 (N-O), 1273, 1147, 1045, 966, 839 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.87 (1H, d, *J* = 8.4 Hz, ArH), 7.74 (1H, d, *J* = 1.8 Hz, ArH), 7.61 (1H, dd, *J* = 8.4, 1.8 Hz, ArH), 6.54-6.41 (2H, m, CH=CH), 2.33-2.25 (2H, m, =CHCH₂), 1.55-1.46 (2H, m, CH₂CH₂CH₃), 1.43-1.36 (2H, m, CH₂CH₃), 0.95 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 145.9 (C), 143.0 (C), 138.0 (CH), 129.3 (CH), 126.9 (CH), 125.8 (CH), 125.0 (CH, q, *J* = 5.5 Hz), 124.2 (C, q *J* = 33.8 Hz), 122.0 (C, q, *J* = 273.4 Hz), 32.8 (CH₂), 30.9 (CH₂), 22.2 (CH₂), 13.8 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -60.5 (3F, s); HRMS (ASAP) Exact mass calcd for C₁₃H₁₄F₃N₁O₂ [M]⁻: 273.0982, found: 273.0982.

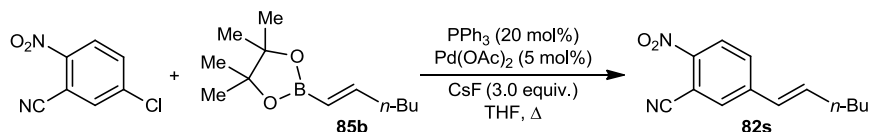
4-[(*E*)-Hex-1-enyl]-2-methyl-1-nitrobenzene (**82r**)



A solution of 5-chloro-2-nitrotoluene (858 mg, 5.00 mmol), alkenylboronic ester **85b**⁷⁵ (1.16 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol), and CsF (2.28 g, 15.0 mmol) in THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane) gave the *alkenylarene* **82r** (407 mg, 31%) as a yellow oil. IR (film) 2958, 2929, 2858, 1604, 1583, 1514 (N-O), 1340 (N-O), 968, 839, 752 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.97 (1H, d, *J* = 8.5 Hz, ArH), 7.31-7.26 (1H,

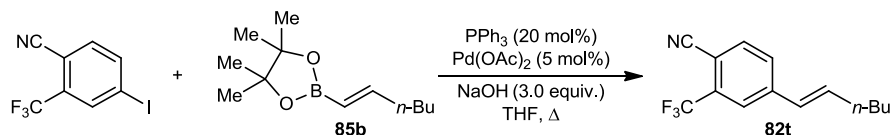
m, ArH), 7.25 (1H, br s, ArH), 6.45-6.34 (2H, m, CH=CH), 2.62 (3H, s, ArCH₃), 2.30-2.22 (2H, m, CH₂CH₂CH₂CH₃), 1.53-1.44 (2H, m, CH₂CH₂CH₃), 1.43-1.34 (2H, m, CH₂CH₃), 0.94 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 147.2 (C), 142.9 (C), 136.0 (CH), 134.3 (C), 130.1 (CH), 128.0 (CH), 125.4 (CH), 123.9 (CH), 32.8 (CH₂), 31.1 (CH₂), 22.2 (CH₂), 21.0 (CH₃), 13.9 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₃H₁₈N₁O₂ [M+H]⁺: 220.1332, found: 220.1329.

5-[(*E*)-Hex-1-enyl]-2-nitrobenzonitrile (**82s**)



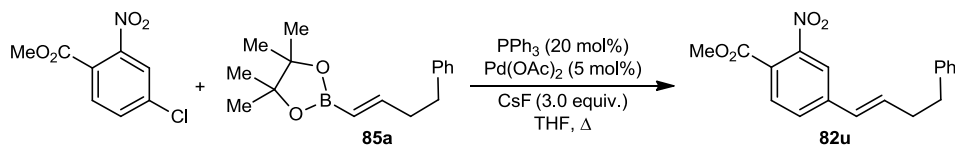
A solution of 5-chloro-2-nitrobenzonitrile (913 mg, 5.00 mmol), alkenylboronic ester **85b**⁷⁵ (1.16 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol), and CsF (2.28 g, 15.0 mmol) in dry THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82s** (727 mg, 63%) as a yellow oil. IR (film) 2929, 2860, 2235 (C≡N), 1647, 1583, 1527, 1466, 1340, 968, 841 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.23 (1H, d, *J* = 8.7 Hz, ArH), 7.79 (1H, d, *J* = 2.0 Hz, ArH), 7.69 (1H, dd, *J* = 8.7, 2.0 Hz, ArH), 6.60-6.51 (1H, m, ArCH=CH), 6.43 (2H, d, *J* = 15.9 Hz, ArCH=CH), 2.33-2.23 (2H, m, CH₂CH₂CH₂CH₃), 1.53-1.43 (2H, m, CH₂CH₂CH₃), 1.41-1.31 (2H, m, CH₂CH₂CH₃), 0.91 (3H, t, *J* = 7.3 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 145.8 (C), 144.5 (C), 139.6 (CH), 132.3 (CH), 130.0 (CH), 126.0 (CH), 125.8 (CH), 115.1 (C), 108.2 (C), 32.7 (CH₂), 30.6 (CH₂), 22.1 (CH₂), 13.7 (CH₃); HRMS (EI) Exact mass calcd for C₁₃H₁₄O₂N₂ [M]⁺: 230.1061, found: 230.1059.

4-[(*E*)-Hex-1-enyl]-2-trifluoromethylbenzonitrile (**82t**)



A solution of 2-trifluoromethyl-4-iodobenzonitrile (1.19 g, 4.00 mmol), alkenylboronic ester **85b**⁷⁵ (925 mg, 4.40 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), PPh₃ (210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) gave the *alkenylarene* **82t** (917 mg, 91%) as a colorless oil. IR (film) 2960, 2931, 2229 (C≡N), 1649 (C=C), 1608, 1323, 1178, 1138, 1053, 966 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.74 (1H, d, *J* = 8.0 Hz, ArH), 7.71 (1H, br s, ArH), 7.58 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 6.53-6.41 (2H, m, CH=CH), 2.31-2.27 (2H, m, =CHCH₂), 1.53-1.47 (2H, m, CH₂CH₂CH₃), 1.42-1.35 (2H, CH₂CH₃), 0.94 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 142.8 (C), 137.8 (CH), 134.7 (CH), 132.7 (C, q, *J* = 32.3 Hz), 128.8 (CH), 127.1 (CH), 123.6 (CH, q, *J* = 4.7 Hz), 122.4 (C, q, *J* = 273.8 Hz), 115.6 (C), 106.9 (C, q, *J* = 2.0 Hz), 32.6 (CH₂), 30.8 (CH₂), 22.1 (CH₂), 13.6 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.5 (3F, s); HRMS (ES) Exact mass calcd for C₁₄H₁₈N₂F₃ [M+NH₄]⁺: 271.1417, found: 271.1415.

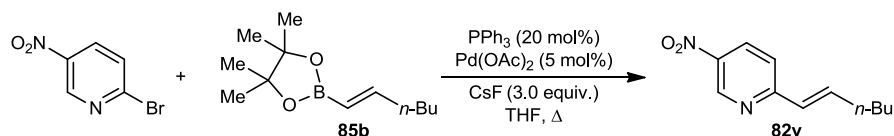
Methyl 4-[(*E*)-hex-1-enyl]-2-nitrobenzoate (**82u**)



A solution of methyl 4-chloro-2-nitrobenzoate (1.08 g, 5.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.16 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol), and CsF (2.28 g, 15.0 mmol) in dry THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and

the combined organic layers were washed with saturated aqueous NH_4Cl solution (80 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% CH_2Cl_2 /hexane \rightarrow 20% CH_2Cl_2 /hexane) gave the *alkenylarene* **82u** (824 mg, 53%) as a colourless oil. IR (film) 3028, 2952, 1732, 1539 (N-O), 1288 (N-O), 1132, 1066, 964, 825, 748 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.74 (1H, d, $J = 1.6$ Hz, ArH), 7.70 (1H, d, $J = 8.0$ Hz, ArH), 7.53 (1H, dd, $J = 8.0, 1.7$ Hz, ArH), 7.37-7.30 (2H, m, ArH), 7.27-7.21 (3H, m, ArH), 6.51-6.39 (2H, m, ArCH=CH), 3.91 (3H, s, OCH_3), 2.87-2.81 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$), 2.65-2.57 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 165.2 (C), 149.1 (C), 142.0 (C), 140.9 (C), 135.4 (CH), 130.2 (CH), 129.3 (CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.5 (CH), 126.0 (CH), 124.2 (C), 120.5 (CH), 52.9 (CH_3), 35.1 (CH_2), 34.6 (CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{18}\text{H}_{21}\text{O}_4\text{N}_2$ $[\text{M}+\text{NH}_4]^+$: 329.1496, found: 329.1499.

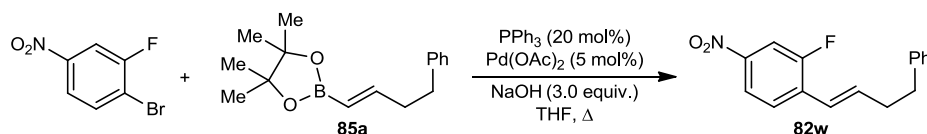
2-[(*E*)-Hex-1-enyl]-5-nitropyridine (**82v**)



A solution of 2-bromo-5-nitropyridine (1.02 g, 5.00 mmol), alkenylboronic ester **85b**⁷⁵ (1.16 g, 5.50 mmol), $\text{Pd}(\text{OAc})_2$ (56 mg, 0.25 mmol), PPh_3 (262 mg, 1.00 mmol), and CsF (2.28 g, 15.0 mmol) in THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et_2O (100 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl solution (80 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (40% CH_2Cl_2 /hexane \rightarrow 60% CH_2Cl_2 /hexane) gave the 2-*alkenylpyridine* **82v** (581 mg, 56%) as a red oil. IR (film) 2958, 2929, 1649, 1593, 1576, 1518 (N-O), 1468, 1348 (N-O), 972, 866 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.30 (1H, s, ArH), 8.35 (1H, dd, $J = 8.7, 2.7$ Hz, ArH), 7.34 (1H, d, $J = 8.7$ Hz, ArH), 7.02 (1H, td, $J = 15.5, 7.1$ Hz, ArCH=CH), 6.55 (1H, d, $J = 15.6$ Hz, ArCH=), 2.30 (2H, app qd, $J = 7.5, 1.4$ Hz, =CH CH_2), 1.55-1.45 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.41-1.34 (2H, m, CH_2CH_3), 0.91 (3H, t, $J = 7.3$ Hz, CH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 161.3 (C), 145.1 (CH), 142.3 (CH),

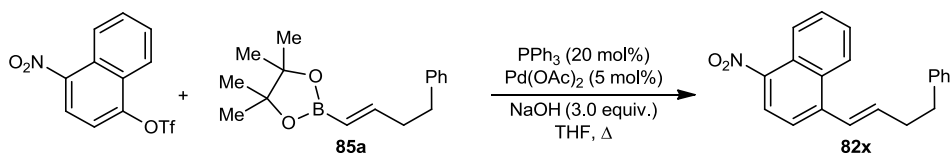
142.1 (C), 131.5 (CH), 128.3 (CH), 120.5 (CH), 32.7 (CH₂), 30.6 (CH₂), 22.2 (CH₂), 13.8 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₁H₁₄N₂O₂ [M]⁻: 206.1061, found: 206.1060.

2-Fluoro-4-nitro-1-[(E)-4-phenylbut-1-enyl]benzene (**82w**)



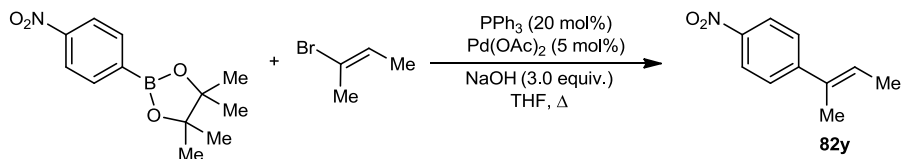
A solution of 4-bromo-3-fluoronitrobenzene (1.32 g, 6.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.70 g, 6.60 mmol), Pd(OAc)₂ (67 mg, 0.30 mmol), PPh₃ (315 mg, 1.20 mmol), and CsF (2.73 g, 18.0 mmol) in THF (60 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) gave the *alkenylarene* **82w** (517 mg, 48%) as a green solid. m.p. 36–38 °C; IR (film) 3028, 2927, 1603, 1523 (N–O), 1348 (N–O), 1232, 970, 806, 741, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.99 (1H, dd, *J* = 8.6, 2.2 Hz, ArH), 7.92 (1H, dd, *J* = 10.2, 2.3 Hz, ArH), 7.60–7.54 (1H, m, ArH), 7.38–7.32 (2H, m, ArH), 7.29–7.23 (3H, m, ArH), 6.67–6.54 (2H, m, CH=CH), 2.91–2.85 (2H, m, CH₂Ph), 2.71–2.62 (2H, m, =CHCH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 158.8 (C, d, *J* = 252.8 Hz), 146.7 (C, d, *J* = 8.9 Hz), 141.0 (C), 137.8 (CH, d, *J* = 4.6 Hz), 132.2 (C, d, *J* = 12.6 Hz), 128.4 (2 x CH), 128.3 (2 x CH), 127.2 (CH, d, *J* = 4.4 Hz), 126.1 (CH), 121.4 (CH, d, *J* = 3.3 Hz), 119.3 (CH, d, *J* = 3.5 Hz), 111.6 (CH, d, *J* = 27.6 Hz), 35.3 (CH₂), 35.2 (CH₂); ¹⁹F NMR (376 MHz, CDCl₃) δ –115.3 (1F, dd, *J* = 10.2, 7.5 Hz); HRMS (EI) Exact mass calcd for C₁₆H₁₄F₁N₁O₂ [M]⁺: 271.1003, found: 271.1004.

1-Nitro-4-[(E)-4-phenylbut-1-enyl]naphthalene (**82x**)



A solution of 4-nitronaphthalen-1-yl trifluoromethanesulfonate¹⁹⁷ (1.93 g, 6.00 mmol), alkenylboronic ester **85a**¹⁹⁵ (1.70 g, 6.60 mmol), Pd(OAc)₂ (67 mg, 0.30 mmol), PPh₃ (315 mg, 1.20 mmol), and NaOH (720 mg, 18.0 mmol) in THF (60 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% CH₂Cl₂/hexane) gave the *alkenylarene* **82x** (980 mg, 54%) as a red solid. m.p. 52-54 °C; IR (film) 3026, 2925, 1572, 1512 (N-O), 1454, 1334 (N-O), 1167, 968, 829, 766 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.61 (1H, d, *J* = 8.7 Hz, ArH), 8.19 (1H, d, *J* = 8.0 Hz, ArH), 8.06 (1H, d, *J* = 8.5 Hz, ArH), 7.75-7.68 (1H, m, ArH), 7.64-7.58 (1H, m, ArH), 7.55 (1H, d, *J* = 8.0 Hz, ArH), 7.37-7.31 (2H, m, ArH), 7.29-7.22 (3H, m, ArH), 7.08 (1H, d, *J* = 15.6 Hz, ArCH=), 6.37 (1H, dt, *J* = 15.6, 6.9 Hz, ArCH=CH), 2.92 (2H, t, *J* = 7.5 Hz, CH₂Ph), 2.76-2.68 (2H, m, CH₂CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 145.4 (C), 142.6 (C), 141.2 (C), 137.1 (CH), 131.7 (C), 129.1 (CH), 128.6 (2 x CH), 128.5 (2 x CH), 127.1 (CH), 127.0 (CH), 126.1 (CH), 125.4 (C), 124.7 (CH), 124.0 (CH), 123.5 (CH), 122.0 (CH), 35.4 (CH₂), 35.2 (CH₂); HRMS (ES) Exact mass calcd for C₂₀H₁₈N₁O₂ [M+H]⁺: 304.1332, found: 304.1335.

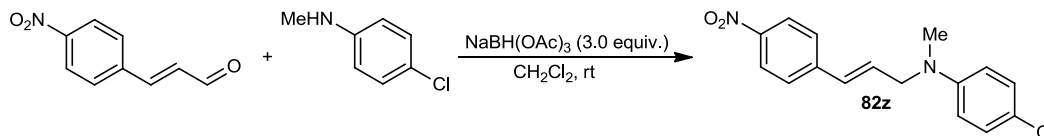
1-[(*E*)-but-2-enyl]-4-nitrobenzene (**82y**)



A solution of 4-nitrophenylboronic acid pinacol ester (996 mg, 4.00 mmol), (*E*)-2-bromo-2-butene (446 μL, 4.40 mmol), Pd(OAc)₂ (45 mg, 0.20 mmol), PPh₃ (210 mg, 0.80 mmol), and NaOH (480 mg, 12.0 mmol) in dry THF (40 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (50 mL) and H₂O (30 mL). The aqueous layer was separated and extracted with Et₂O (2 x 40 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by

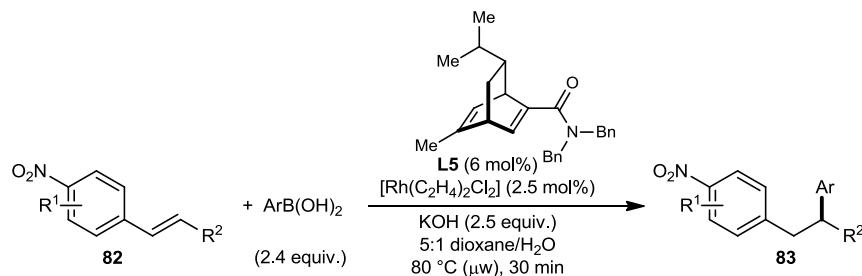
column chromatography (10% CH₂Cl₂/hexane→30% CH₂Cl₂/hexane) gave the *alkenylarene* **82y** (577 mg, 81%) as a yellow liquid. IR (film) 2920, 1595, 1514 (N-O), 1344, 1107, 1057, 854, 825, 750, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.17-8.11 (2H, m, ArH), 7.51-7.45 (2H, m, ArH), 6.10-6.01 (1H, m, =CH), 2.08-2.03 (3H, m, ArCCH₃), 1.85 (3H, dd, *J* = 6.9, 1.1 Hz, =CHCH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 150.3 (C), 146.2 (C), 134.0 (C), 126.8 (CH), 125.9 (2 x CH), 123.5 (2 x CH), 15.1 (CH₃), 14.5 (CH₃); HRMS (APCI) Exact mass calcd for C₁₀H₁₁N₁O₂ [M+H]⁺: 178.0863, found: 178.0858.

(4-Chlorophenyl)methyl-[(*E*)-3-(4-nitrophenyl)allyl]amine (82z)

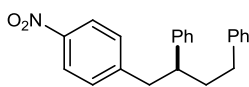


A solution of *trans*-4-nitrocinnamaldehyde (532 mg, 3.00 mmol) and 4-chloro-*N*-methylaniline (363 μL, 3.00 mmol) in CH₂Cl₂ (20 mL) was stirred at room temperature for 2 h. NaBH(OAc)₃ (1.91 g, 9.00 mmol) was added in one portion and the reaction was stirred for a further 3 h. The mixture was partitioned between CH₂Cl₂ (20 mL) and H₂O (10 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 20 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ solution (20 mL), brine (20 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH₂Cl₂/hexane→50% CH₂Cl₂/hexane) gave the *alkenylarene* **82z** (800 mg, 88%) as a yellow solid. m.p. 88-90 °C; IR (film) 2896, 1594, 1501 (N-O), 1341 (N-O), 1211, 1110, 968, 859, 810, 737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.20-8.13 (2H, m, ArH), 7.50-7.44 (2H, m, ArH), 7.22-7.16 (2H, m, ArH), 6.71-6.64 (2H, m, ArH), 6.55 (1H, d, *J* = 16.0 Hz, ArCH=), 6.42 (1H, dt, *J* = 16.0, 4.9 Hz, ArCH=CH), 4.12 (2H, dd, *J* = 4.9, 1.5 Hz, CH₂N), 3.01 (3H, s, NCH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 147.7 (C), 146.8 (C), 143.1 (C), 130.6 (CH), 129.2 (CH), 129.0 (2 x CH), 126.8 (2 x CH), 124.0 (2 x CH), 121.7 (C), 113.6 (2 x CH), 54.9 (CH₂), 38.5 (CH₃); *m/z* (EI) 302 ([M]⁺, 41), 207 (47), 116 (100).

Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Alkenylarenes: General Procedure A



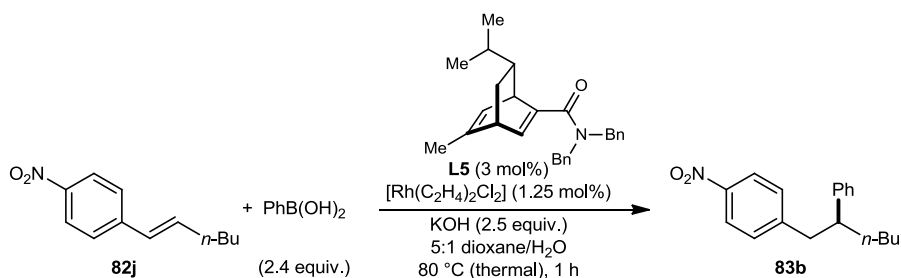
A solution of $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 0.005 mmol) and ligand **L5** (4.6 mg, 0.012 mmol) in dioxane (0.3 mL) was stirred under nitrogen at room temperature for 15 min. This solution was then added *via* cannula to a sealed nitrogen-flushed microwave vial containing the appropriate alkenylarene (0.20 mmol), the appropriate arylboronic acid (0.48 mmol), KOH (28 mg, 0.50 mmol), and H_2O (0.1 mL), using further dioxane (0.2 mL) as a rinse. The resulting mixture was irradiated in a microwave reactor at 80 °C for 30 min. After cooling to room temperature, the mixture was filtered through a short plug of SiO_2 using CH_2Cl_2 as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography gave the arylated product.

 **1-[(S)-2,4-Diphenylbutyl]-4-nitrobenzene (83a).** *Using microwave irradiation:* The title compound was prepared according to the General Procedure A from alkenylarene **82a** (51 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (5% CH_2Cl_2 /hexane \rightarrow 20% CH_2Cl_2 /hexane) to give a yellow oil (61 mg, 92%). $[\alpha]_D^{24} +72.9$ (c 0.85, $CHCl_3$); IR (film) 3026, 2927, 2856, 1603, 1518 (N-O), 1452, 1344 (N-O), 852, 758, 700 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.06-7.99 (2H, m, ArH), 7.34-7.15 (6H, m, ArH), 7.13-7.05 (6H, m, ArH), 3.06 (1H, dd, $J = 13.2, 6.3$ Hz, ArCH₂CH), 2.96 (1H, dd, $J = 13.2, 8.5$ Hz, ArCH₂CH), 2.92-2.81 (1H, m, ArCH₂CH), 2.60-2.40 (2H, m, CH₂CH₂Ph), 2.10-1.99 (2H, m, CH₂CH₂Ph); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.3 (C), 146.3 (C), 143.2 (C), 141.9 (C), 129.8 (2 x CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.3 (2 x CH), 127.7 (2 x CH), 126.6 (CH), 125.8 (CH), 123.3 (2 x CH), 47.2 (CH), 43.7 (CH₂), 37.5 (CH₂), 33.6 (CH₂); HRMS (ES) Exact mass calcd for $C_{22}H_{25}N_2O_2$ $[M+NH_4]^+$:

349.1911, found: 349.1911. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 18.1 min, t_r (minor) = 19.9 min; 95% ee.

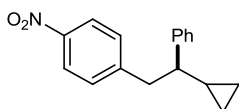
Using thermal heating: A repeat of the above reaction using thermal heating (oil bath temperature 80 °C) under otherwise identical conditions gave the alkenylarene **83a** (60 mg, 90%) in 94% ee.

1-Nitro-4-[(*S*)-2-phenylhexyl]benzene (**83b**)

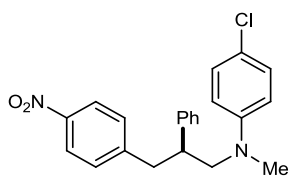


A solution of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (4.9 mg, 0.0125 mmol) and ligand **L5** (11.6 mg, 0.030 mmol) in dioxane (1.5 mL) was stirred under nitrogen at room temperature for 15 min. This solution was then added *via* cannula to a sealed nitrogen-flushed microwave vial containing alkenylarene **82j** (205 mg, 1.00 mmol), phenylboronic acid (293 mg, 2.40 mmol), KOH (140 mg, 2.50 mmol), and H_2O (0.5 mL), using further dioxane (1.0 mL) as a rinse. The resulting mixture was heated to 80 °C in an oil bath for 1 h. After cooling to room temperature, the mixture was filtered through a short plug of SiO_2 using CH_2Cl_2 as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (5% CH_2Cl_2 /hexane \rightarrow 20% CH_2Cl_2 /hexane) gave the arylation product **83b** (236 mg, 83%) as a yellow oil. $[\alpha]_{\text{D}}^{24} +137.0$ (c 1.07, CHCl_3); IR (film) 2956, 2929, 2858, 1603, 1518 (N-O), 1346 (N-O), 1109, 850, 760, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.07–8.01 (2H, m, ArH), 7.30–7.23 (2H, m, ArH), 7.22–7.16 (1H, m, ArH), 7.15–7.10 (2H, m, ArH), 7.09–7.04 (2H, m, ArH), 3.06 (1H, dd, J = 13.3, 6.1 Hz, ArCH₂), 2.94 (1H, dd, J = 13.3, 8.8 Hz, ArCH₂), 2.88–2.78 (1H, m, ArCH₂CH), 1.71 (2H, app q, J = 7.6 Hz, CH₂CH₂CH₂CH₃), 1.37–1.10 (4H, m, CH₂CH₂CH₃), 0.84 (3H, t, J = 7.2 Hz, CH₃); ^{13}C NMR (125.8 MHz, CDCl_3) δ 148.7 (C), 146.2 (C), 143.8 (C), 129.8 (2 x CH), 128.3 (2 x CH), 127.6 (2 x CH), 126.3 (CH), 123.2 (2 x CH), 47.9 (CH), 43.6 (CH₂), 35.6 (CH₂),

29.6 (CH₂), 22.6 (CH₂), 13.9 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₈H₂₂N₁O₂ [M+H]⁺: 284.1645, found: 284.1646. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 8.2 min, t_r (minor) = 9.2 min; 95% ee.

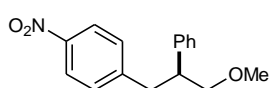


1-[(R)-2-Cyclopropyl-2-phenylethyl]-4-nitrobenzene (83c). The title compound was prepared according to the General Procedure A from alkenylarene **82k** (38 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (40 mg, 74%). [α]_D²⁴ +49.4 (c 0.89, CHCl₃); IR (film) 3078, 3001, 2925, 1599, 1516 (N-O), 1344 (N-O), 1109, 1018, 750, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.08-8.03 (2H, m, ArH), 7.32-7.26 (2H, m, ArH), 7.25-7.20 (1H, m, ArH), 7.18-7.09 (4H, m, ArH), 3.23 (1H, dd, J = 13.3, 6.2 Hz, ArCH₂), 3.13 (1H, dd, J = 13.3, 8.4 Hz, ArCH₂), 2.15-2.07 (1H, m, ArCH₂CH), 1.18-1.06 (1H, m, CHCH₂CH₂), 0.65-0.57 (1H, m, CH₂CH₂), 0.50-0.42 (1H, m, CH₂CH₂), 0.17-0.11 (2H, m, CH₂CH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 148.4 (C), 146.3 (C), 143.8 (C), 130.0 (2 x CH), 128.3 (2 x CH), 127.6 (2 x CH), 126.5 (CH), 123.2 (2 x CH), 52.9 (CH), 43.4 (CH₂), 16.8 (CH), 5.9 (CH₂), 4.0 (CH₂); HRMS (EI) Exact mass calcd for C₁₇H₁₇N₁O₂ [M]⁺: 267.1254, found: 267.1252. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 9.3 min, t_r (major) = 10.2 min; 92% ee.



(4-Chlorophenyl)methyl-[(S)-3-(4-nitrophenyl)-2-phenylpropyl]amin (83d). The title compound was prepared according to the General Procedure A from alkenylarene **82z** (61 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (20% CH₂Cl₂/hexane→40% CH₂Cl₂/hexane) to give a yellow gum (65 mg, 85%). [α]_D²⁴ -28.7 (c 1.05, CHCl₃); IR (film) 1597, 1510, 1500 (N-O), 1344 (N-O), 1235, 1110, 848, 808, 766, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.06-8.00 (2H, m, ArH), 7.30-7.24 (2H, m, ArH), 7.24-7.19 (1H, m, ArH), 7.18-7.12 (4H, m, ArH), 7.11-7.06 (2H, m, ArH), 6.53-6.47 (2H, m, ArH), 3.70 (1H, dd, J = 14.8,

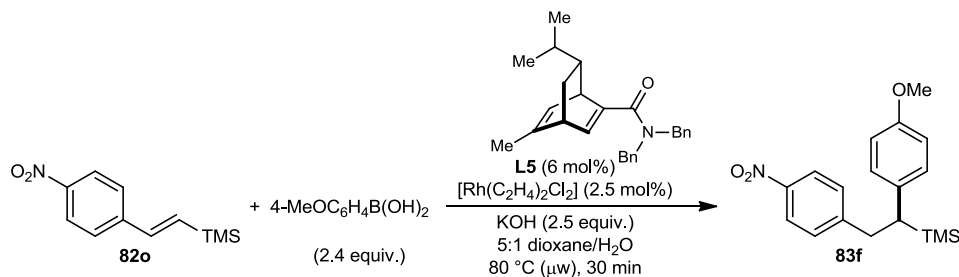
7.0 Hz, CH_2N), 3.46 (1H, dd, $J = 14.8, 7.6$ Hz, CH_2N), 3.34-3.24 (1H, m, ArCH_2CH), 3.16 (1H, dd, $J = 13.6, 5.5$ Hz, ArCH_2), 3.02 (1H, dd, $J = 13.6, 9.8$ Hz, ArCH_2), 2.72 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 147.8 (C), 147.3 (C), 146.4 (C), 141.4 (C), 129.7 (2 x CH), 129.0 (2 x CH), 128.7 (2 x CH), 127.8 (2 x CH), 127.1 (CH), 123.4 (2 x CH), 121.2 (C), 113.1 (2 x CH), 59.3 (CH_2), 46.0 (CH), 39.8 (CH_2), 39.7 (CH_3); m/z (ES) 381 ($[\text{M}+\text{H}]^+$, 100). Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 18.0 min, t_r (major) = 19.8 min; 91% ee.



1-[(*S*)-3-Methoxy-2-phenylpropyl]-4-nitrobenzene (83e). The

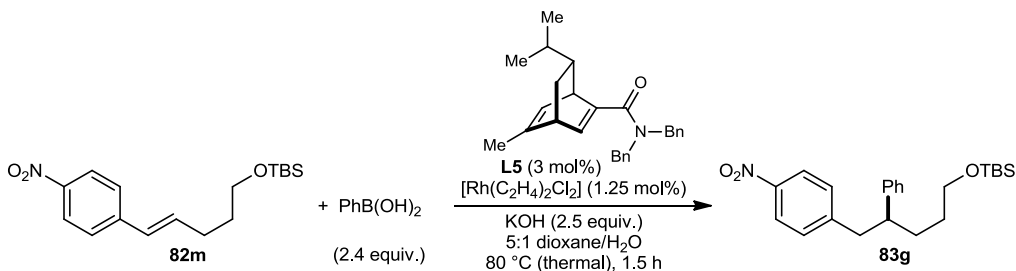
title compound was prepared according to the General Procedure A from alkenylarene **82i** (39 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (40% CH_2Cl_2 /hexane) to give a colorless oil (45 mg, 82%). $[\alpha]_D^{24} +106.0$ (c 1.00, CHCl_3); IR (film) 2921, 1644, 1604, 1516 (N-O), 1494, 1453, 1343 (N-O), 1110, 760, 699 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.07-8.01 (2H, m, ArH), 7.31-7.24 (2H, m, ArH), 7.24-7.18 (1H, m, ArH), 7.18-7.13 (2H, m, ArH), 7.13-7.07 (2H, m, ArH), 3.58-3.56 (2H, m, CH_2O), 3.37 (3H, s, OCH_3), 3.29 (1H, dd, $J = 13.3, 5.5$ Hz, ArCH_2), 3.21-3.10 (1H, m, ArCH_2CH), 2.96 (1H, dd, $J = 13.3, 9.1$ Hz, ArCH_2); ^{13}C NMR (100.6 MHz, CDCl_3) δ 148.2 (C), 146.3 (C), 141.1 (C), 129.9 (2 x CH), 128.5 (2 x CH), 127.8 (2 x CH), 126.9 (CH), 123.3 (2 x CH), 76.0 (CH_2), 58.9 (CH_3), 47.7 (CH), 39.1 (CH_2); m/z (ES) 294 ($[\text{M}+\text{Na}]^+$, 100). Enantiomeric excess was determined by HPLC with a Chiralcel AS-H column (99:1 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 19.8 min, t_r (major) = 21.0 min; 91% ee.

[(*S*)-1-(4-Methoxyphenyl)-2-(4-nitrophenyl)ethyl]trimethylsilane (83f)



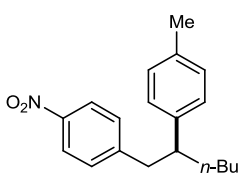
A solution of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (3.8 mg, 0.010 mmol) and ligand **L5** (9.2 mg, 0.024 mmol) in dioxane (0.6 mL) was stirred under nitrogen at room temperature for 15 min. This solution was then added *via* cannula to a sealed nitrogen-flushed microwave vial containing alkenylarene **82o** (89 mg, 0.40 mmol), 4-methoxyphenylboronic acid (146 mg, 0.96 mmol), KOH (56 mg, 1.00 mmol), and H_2O (0.2 mL), using further dioxane (0.4 mL) as a rinse. The resulting mixture was irradiated in a microwave reactor at 80 °C for 30 min. After cooling to room temperature, the mixture was filtered through a short plug of SiO_2 using CH_2Cl_2 as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH_2Cl_2 /hexane→40% CH_2Cl_2 /hexane) gave the *arylation product* **83f** (75 mg, 57%) as a yellow oil. $[\alpha]_{\text{D}}^{24} +142.2$ (*c* 0.97, CHCl_3); IR (film) 2953, 1605, 1509 (N-O), 1344 (N-O), 1247, 1178, 1108, 1037, 856, 841 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.03-7.97 (2H, m, ArH), 7.20-7.14 (2H, m, ArH), 6.91-6.84 (2H, m, ArH), 6.78-6.71 (2H, m, ArH), 3.75 (3H, s, OCH_3), 3.15 (1H, dd, $J = 14.5, 4.2$ Hz, ArCH_2), 3.09 (1H, dd, $J = 14.5, 11.8$ Hz, ArCH_2), 2.30 (1H, dd, $J = 11.8, 4.2$ Hz, ArCH_2CH), 0.02 (9H, s, $\text{Si}(\text{CH}_3)_3$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 157.0 (C), 150.0 (C), 146.1 (C), 133.6 (C), 129.2 (2 x CH), 128.6 (2 x CH), 123.3 (2 x CH), 113.7 (2 x CH), 55.1 (CH_3), 37.6 (CH), 36.0 (CH_2), -2.9 (3 x CH_3); m/z (ES) 352 ($[\text{M}+\text{Na}]^+$, 100). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_{r} (major) = 8.4 min, t_{r} (minor) = 9.1 min; 91% ee.

4-[(*S*)-5-*tert*-Butyldimethylsilyloxy-2-phenylpentyl]-1-nitrobenzene (**83g**)



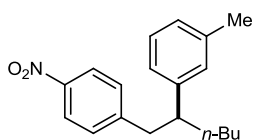
A solution of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (24 mg, 0.0625 mmol) and ligand **L5** (58 mg, 0.15 mmol) in dioxane (7.5 mL) was stirred under nitrogen at room temperature for 15 min. This solution was then added *via* cannula to a sealed nitrogen-flushed microwave vial containing alkenylarene **82m** (1.61 g, 5.00 mmol), phenylboronic acid (1.46 g, 12.0

mmol), KOH (701 mg, 2.50 mmol), and H₂O (2.5 mL), using further dioxane (5.0 mL) as a rinse. The resulting mixture was heated to 80 °C in an oil bath for 1.5 h. After cooling to room temperature, the mixture was filtered through a short plug of SiO₂ using CH₂Cl₂ as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) gave the *arylation product* **83g** (1.75 g, 88%) as a yellow oil. $[\alpha]_{\text{D}}^{24} +79.3$ (*c* 1.12, CHCl₃); IR (film) 2929, 2856, 1603, 1520 (N-O), 1346 (N-O), 1255, 1105, 837, 775, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.09-8.02 (2H, m, ArH), 7.31-7.24 (2H, m, ArH), 7.23-7.17 (1H, m, ArH), 7.17-7.12 (2H, m, ArH), 7.11-7.05 (2H, m, ArH), 3.61-3.51 (2H, m, CH₂O), 3.06 (1H, dd, *J* = 13.3, 6.4 Hz, ArCH₂), 2.97 (1H, dd, *J* = 13.3, 8.4 Hz, ArCH₂), 2.91-2.81 (1H, m, ArCH₂CH), 1.85-1.78 (1H, m, CH₂CH₂CH₂O), 1.75-1.68 (1H, m, CH₂CH₂CH₂O), 1.48-1.36 (2H, m, CH₂CH₂O), 0.89 (9H, s, C(CH₃)₃), 0.02 (3H, s, SiCH₃), 0.01 (3H, s, SiCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 148.6 (C), 146.3 (C), 143.6 (C), 129.8 (2 x CH), 128.4 (2 x CH), 127.6 (2 x CH), 126.4 (CH), 123.2 (2 x CH), 62.8 (CH₂), 47.6 (CH), 43.7 (CH₂), 31.9 (CH₂), 30.6 (CH₂), 25.9 (3 x CH₃), 18.3 (C), -5.4 (2 x CH₃); HRMS (ES) Exact mass calcd for C₂₃H₃₄N₁O₃Si₁ [M+H]⁺: 400.2302, found: 400.2306. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); *t*_r (major) = 7.1 min, *t*_r (minor) = 7.8 min; 93% ee.

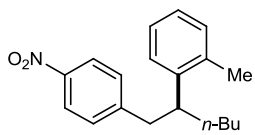


4-[(S)-2-(4-Methylphenyl)hexyl]-1-nitrobenzene (83h). The title compound was prepared according to the General Procedure A from alkenylarene **82j** (41 mg, 0.20 mmol) and 4-methylphenylboronic acid (65 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (52 mg, 87%). $[\alpha]_{\text{D}}^{24} +154.6$ (*c* 0.97, CHCl₃); IR (film) 2956, 2927, 2858, 1603, 1518 (N-O), 1344 (N-O), 1109, 852, 818, 405 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.06-8.01 (2H, m, ArH), 7.15-7.09 (2H, m, ArH), 7.06 (2H, d, *J* = 7.8 Hz, ArH), 6.97-6.92 (2H, m, ArH), 3.02 (1H, dd, *J* = 13.3, 6.2 Hz, ArCH₂), 2.91 (1H, dd, *J* = 13.3, 8.7 Hz, ArCH₂), 2.83-2.73 (1H, m, ArCH₂CH), 2.31 (3H, s, ArCH₃), 1.70-1.63 (2H, m, CH₂CH₂CH₂CH₃), 1.35-1.09 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ

148.9 (C), 146.2 (C), 140.8 (C), 135.8 (C), 129.8 (2 x CH), 129.0 (2 x CH), 127.5 (2 x CH), 123.2 (2 x CH), 47.4 (CH), 43.7 (CH₂), 35.7 (CH₂), 29.7 (CH₂), 22.6 (CH₂), 21.0 (CH₃), 13.9 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₂₇N₂O₂ [M+NH₄]⁺: 315.2067, found: 315.2068. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99.3:0.7 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 8.2 min, t_r (minor) = 9.0 min; 94% ee.

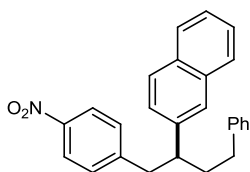


4-[(S)-2-(3-Methylphenyl)hexyl]-1-nitrobenzene (83i). The title compound was prepared according to the General Procedure A from alkenylarene **82j** (41 mg, 0.20 mmol) and 3-methylphenylboronic acid (65 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (53 mg, 90%). [α]_D²⁴ +130.9 (*c* 0.83, CHCl₃); IR (film) 2927, 2858, 1604, 1518 (N-O), 1456, 1344 (N-O), 1109, 860, 781, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07-8.02 (2H, m, ArH), 7.17-7.10 (3H, m, ArH), 7.00 (1H, d, *J* = 7.5 Hz, ArH), 6.89-6.82 (2H, m, ArH), 3.01 (1H, dd, *J* = 13.4, 6.4 Hz, ArCH₂), 2.93 (1H, dd, *J* = 13.4, 8.4 Hz, ArCH₂), 2.82-2.72 (1H, m, ArCH₂CH), 2.31 (3H, s, ArCH₃), 1.70-1.62 (2H, m, CH₂CH₂CH₂CH₃), 1.35-1.08 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 148.9 (C), 146.2 (C), 143.9 (C), 137.9 (C), 129.8 (2 x CH), 128.4 (CH), 128.2 (CH), 127.1 (CH), 124.6 (CH), 123.2 (2 x CH), 47.8 (CH), 43.6 (CH₂), 35.6 (CH₂), 29.7 (CH₂), 22.6 (CH₂), 21.5 (CH₃), 13.9 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₉H₂₄N₁O₂ [M+H]⁺: 298.1802, found: 298.1804. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99.3:0.7 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 8.0 min, t_r (minor) = 8.7 min; 92% ee.

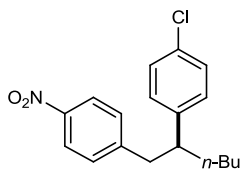


4-[(S)-2-(2-Methylphenyl)hexyl]-1-nitrobenzene (83j). The title compound was prepared according to the General Procedure A from alkenylarene **82j** (41 mg, 0.20 mmol) and 2-methylphenylboronic acid (65 mg, 0.48 mmol) but for a reaction time of 1 h and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (36 mg, 61%). [α]_D²⁴ +107.9 (*c* 0.95, CHCl₃); IR (film) 2929, 2858, 1603, 1518 (N-O), 1462,

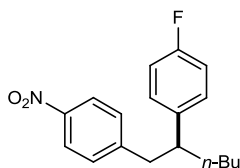
1344 (N-O), 1109, 852, 760, 727 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.06-8.00 (2H, m, ArH), 7.26-7.18 (2H, m, ArH), 7.13-7.01 (4H, m, ArH), 3.22-3.11 (1H, m, ArCH_2CH), 3.02 (1H, dd, $J = 13.2, 6.0$ Hz, ArCH_2), 2.90 (1H, dd, $J = 13.2, 8.8$ Hz, ArCH_2), 2.04 (3H, s, ArCH_3), 1.69-1.64 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.35-1.09 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.84 (3H, t, $J = 7.2$ Hz, CH_2CH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 148.8 (C), 146.2 (C), 142.2 (C), 136.1 (C), 130.2 (CH), 129.8 (2 x CH), 126.2 (CH), 125.9 (CH), 125.7 (CH), 123.2 (2 x CH), 43.5 (CH_2), 42.0 (CH), 35.7 (CH_2), 29.6 (CH_2), 22.8 (CH_2), 19.7 (CH_3), 13.9 (CH_3); HRMS (ASAP) Exact mass calcd for $\text{C}_{19}\text{H}_{24}\text{N}_1\text{O}_2$ $[\text{M}+\text{H}]^+$: 298.1802, found: 298.1804. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 7.3 min, t_r (minor) = 8.3 min; 97% ee.



2-[(S)-1-(4-Nitrobenzyl)-3-phenylpropyl]naphthalene (83k). The title compound was prepared according to the General Procedure A from alkenylarene **82a** (51 mg, 0.20 mmol) and 2-naphthylboronic acid (83 mg, 0.48 mmol) and purified by column chromatography (5% CH_2Cl_2 /hexane \rightarrow 20% CH_2Cl_2 /hexane) to give a dark brown viscous oil (60 mg, 79%). $[\alpha]_{\text{D}}^{24} +108.0$ (c 0.69, CHCl_3); IR (film) 3057, 2933, 1601, 1518 (N-O), 1454, 1344 (N-O), 1109, 858, 746, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.03-7.97 (2H, m, ArH), 7.87-7.80 (2H, m, ArH), 7.79-7.47 (1H, m, ArH), 7.52-7.43 (3H, m, ArH), 7.33-7.24 (3H, m, ArH), 7.22-7.16 (1H, m, ArH), 7.13-7.04 (4H, m, ArH), 3.19-3.00 (3H, m, ArCH_2CH), 2.60-2.43 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$), 2.21-2.06 (2H, m, $\text{CH}_2\text{CH}_2\text{Ph}$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 148.2 (C), 146.3 (C), 141.8 (C), 140.6 (C), 133.4 (C), 132.4 (C), 129.8 (2 x CH), 128.34 (2 x CH), 128.31 (2 x CH), 127.6 (CH), 127.5 (CH), 126.7 (CH), 126.1 (CH), 125.9 (CH), 125.5 (2 x CH), 123.3 (2 x CH), 47.3 (CH), 43.5 (CH_2), 37.4 (CH_2), 33.6 (CH_2); m/z (ES) 404 ($[\text{M}+\text{Na}]^+$, 100). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 225 nm, 25 °C); t_r (minor) = 45.2 min, t_r (major) = 48.3 min; 89% ee.

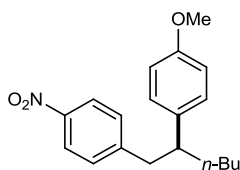


4-[(S)-2-(4-Chlorophenyl)hexyl]-1-nitrobenzene (83l). The title compound was prepared according to the General Procedure A from alkenylarene **82j** (41 mg, 0.20 mmol) and 4-chlorophenylboronic acid (75 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (56 mg, 89%). [α]_D²⁴ +158.6 (*c* 0.90, CHCl₃); IR (film) 2927, 2858, 1601, 1518 (N-O), 1491, 1454, 1344 (N-O), 1093, 1014, 829 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07-8.02 (2H, m, ArH), 7.25-7.19 (2H, m, ArH), 7.13-7.08 (2H, m, ArH), 7.01-6.95 (2H, m, ArH), 3.04 (1H, dd, *J* = 13.2, 5.8 Hz, ArCH₂), 2.88 (1H, dd, *J* = 13.2, 9.0 Hz, ArCH₂), 2.84-2.75 (1H, m, ArCH₂CH), 1.75-1.59 (2H, m, CH₂CH₂CH₂CH₃), 1.35-1.06 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 148.2 (C), 146.3 (C), 142.3 (C), 132.0 (C), 129.8 (2 x CH), 128.9 (2 x CH), 128.5 (2 x CH), 123.3 (2 x CH), 47.4 (CH), 43.5 (CH₂), 35.6 (CH₂), 29.6 (CH₂), 22.6 (CH₂), 13.9 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₈H₂₀ClN₁O₂ [M]⁻: 317.1188, found: 317.1186. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 12.3 min, t_r (minor) = 13.3 min; 94% ee.



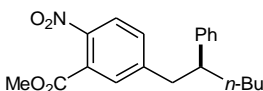
4-[(S)-2-(4-Fluorophenyl)hexyl]-1-nitrobenzene (83m). The title compound was prepared according to the General Procedure A from alkenylarene **82j** (41 mg, 0.20 mmol) and 4-fluorophenylboronic acid (67 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (49 mg, 81%). [α]_D²⁴ +119.1 (*c* 0.94, CHCl₃); IR (film) 2929, 2858, 1603, 1510 (N-O), 1346 (N-O), 1223, 1159, 1109, 835, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07-8.01 (2H, m, ArH), 7.13-7.06 (2H, m, ArH), 7.03-6.89 (4H, m, ArH), 3.04 (1H, dd, *J* = 12.8, 5.5 Hz, ArCH₂), 2.92-2.75 (2H, m, ArCH₂CH), 1.77-1.58 (2H, m, CH₂CH₂CH₂CH₃), 1.37-1.05 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, *J* = 7.2 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 161.4 (C, d, *J* = 244.3 Hz), 148.4 (C), 146.3 (C), 139.4 (C, d, *J* = 3.2 Hz), 129.8 (2 x CH), 128.9 (2 x CH, d, *J* = 7.7 Hz), 123.3 (2 x CH), 115.2 (2 x CH, d, *J* = 21.1 Hz), 47.2 (CH), 43.7 (CH₂), 35.8 (CH₂), 29.6 (CH₂), 22.6 (CH₂), 13.9 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -117.0 (1F, tt, *J* = 8.6, 5.5 Hz); HRMS (ASAP) Exact mass calcd for C₁₈H₂₀F₁N₁O₂ [M]⁻:

301.1484, found: 301.1483. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 11.5 min, t_r (minor) = 12.5 min; 94% ee.



4-[(S)-2-(4-Methoxyphenyl)hexyl]-1-nitrobenzene (83n). The title

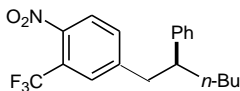
compound was prepared according to the General Procedure A from alkenylarene **82j** (41 mg, 0.20 mmol) and 4-methoxyphenylboronic acid (73 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow amorphous solid (52 mg, 83%). $[\alpha]_D^{24}$ +147.6 (*c* 0.75, CHCl₃); IR (film) 2929, 2856, 1606, 1514 (N-O), 1344 (N-O), 1248, 1178, 1038, 831, 748 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.06-8.01 (2H, m, ArH), 7.13-7.07 (2H, m, ArH), 6.98-6.92 (2H, m, ArH), 6.81-6.76 (2H, m, ArH), 3.78 (3H, s, OCH₃), 3.01 (1H, dd, *J* = 13.3, 5.9 Hz, ArCH₂), 2.88 (1H, dd, *J* = 13.3, 8.9 Hz, ArCH₂), 2.81-2.71 (1H, m, ArCH₂CH), 1.73-1.59 (2H, m, CH₂CH₂CH₂CH₃), 1.35-1.09 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 158.0 (C), 148.9 (C), 146.2 (C), 135.8 (C), 129.8 (2 x CH), 128.5 (2 x CH), 123.2 (2 x CH), 113.7 (2 x CH), 55.2 (CH₃), 47.1 (CH), 43.8 (CH₂), 35.9 (CH₂), 29.7 (CH₂), 22.6 (CH₂), 14.0 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₉H₂₃N₁O₃ [M]⁺: 313.1683, found: 313.1688. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (98:2 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 10.8 min, t_r (minor) = 12.2 min; 93% ee.



2-Nitro-5-[(S)-2-phenylhexyl]benzoic acid methyl ester (83o).

The title compound was prepared according to the General Procedure A from alkenylarene **82p** (53 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a colorless oil (54 mg, 80%). $[\alpha]_D^{24}$ +90.0 (*c* 0.76, CHCl₃); IR (film) 2929, 1738 (C=O), 1645, 1527 (N-O), 1437, 1348 (N-O), 1294, 1205, 1070, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.74 (1H, d, *J* = 8.3 Hz, ArH), 7.32 (1H, d, *J* = 1.8 Hz, ArH), 7.29-7.23 (2H, m, ArH), 7.22-7.16 (1H, m, ArH), 7.10 (1H, dd, *J* = 8.3, 1.9 Hz, ArH), 7.07-7.02 (2H, m, ArH), 3.91 (3H, s, OCH₃), 3.03 (1H, dd, *J* = 13.4, 6.1 Hz,

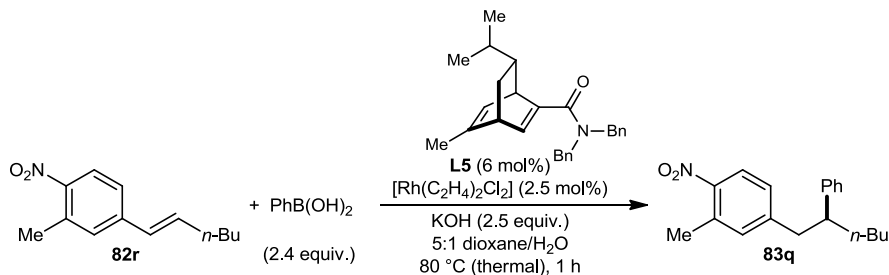
ArCH₂), 2.92 (1H, dd, $J = 13.4, 8.7$ Hz, ArCH₂), 2.85-2.75 (1H, m, ArCH₂CH), 1.69 (2H, app q, $J = 7.6$ Hz, CH₂CH₂CH₂CH₃), 1.35-1.05 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, $J = 7.2$ Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 166.3 (C), 147.3 (C), 145.8 (C), 143.5 (C), 131.9 (CH), 130.1 (CH), 128.5 (2 x CH), 127.7 (C), 127.6 (2 x CH), 126.5 (CH), 123.7 (CH), 53.2 (CH₃), 47.8 (CH), 43.4 (CH₂), 35.6 (CH₂), 29.7 (CH₂), 22.6 (CH₂), 13.9 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₇N₂O₄ [M+NH₄]⁺: 359.1965, found: 359.1965. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 19.7 min, t_r (minor) = 23.2 min; 91% ee.



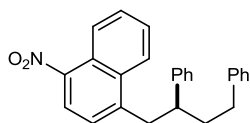
1-Nitro-4-[(S)-2-phenylhexyl]-2-trifluoromethylbenzene (83p).

The title compound was prepared according to the General Procedure A from alkenylarene **82q** (55 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a colorless oil (60 mg, 85%). [α]_D²⁴ +89.7 (c 0.98, CHCl₃); IR (film) 2931, 1643, 1539 (N-O), 1454, 1358 (N-O), 1313, 1176, 1144, 1049, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.71 (1H, d, $J = 8.3$ Hz, ArH), 7.34 (1H, d, $J = 1.4$ Hz, ArH), 7.30-7.17 (4H, m, ArH), 7.07-7.00 (2H, m, ArH), 3.09 (1H, dd, $J = 13.4, 5.7$ Hz, ArCH₂), 2.95 (1H, dd, $J = 13.4, 9.2$ Hz, ArCH₂), 2.85-2.75 (1H, m, ArCH₂CH), 1.79-1.66 (2H, m, CH₂CH₂CH₂CH₃), 1.38-1.11 (4H, m, CH₂CH₂CH₃), 0.85 (3H, t, $J = 7.2$ Hz, CH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 146.9 (C), 146.0 (C), 143.1 (C), 133.2 (CH), 128.5 (CH), 128.4 (CH, q, $J = 5.4$ Hz), 127.6 (CH), 126.7 (CH), 124.9 (CH), 123.3 (C, q, $J = 33.7$ Hz), 121.9 (C, q, $J = 273.4$ Hz), 47.8 (CH), 43.4 (CH₂), 35.6 (CH₂), 29.6 (CH₂), 22.6 (CH₂), 13.9 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -60.4 (3F, s); HRMS (ASAP) Exact mass calcd for C₁₉H₂₁F₃N₁O₂ [M+H]⁺: 352.1519, found: 352.1521. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 8.9 min, t_r (minor) = 10.0 min; 92% ee.

2-Methyl-1-nitro-4-[(S)-2-phenylhexyl]benzene (83q)

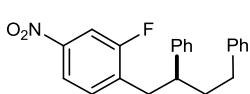


A solution of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (9.8 mg, 0.025 mmol) and ligand **L5** (23 mg, 0.060 mmol) in dioxane (2.0 mL) was stirred under nitrogen at room temperature for 15 min. This solution was then added *via* cannula to a sealed nitrogen-flushed microwave vial containing alkenylarene **82r** (219 mg, 1.00 mmol), phenylboronic acid (293 mg, 2.40 mmol), KOH (140 mg, 2.50 mmol), and H_2O (0.5 mL), using further dioxane (0.5 mL) as a rinse. The resulting mixture was irradiated in a microwave reactor at 80 °C for 30 min. After cooling to room temperature, the mixture was filtered through a short plug of SiO_2 using CH_2Cl_2 as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (20% CH_2Cl_2 /hexane) gave the arylation product **83q** (235 mg, 79%) as a yellow oil. $[\alpha]_{\text{D}}^{24} +104.7$ (*c* 1.05, CHCl_3); IR (film) 2956, 2929, 2858, 1610, 1587, 1516 (N-O), 1452, 1342 (N-O), 837, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.87-7.81 (1H, m, ArH), 7.31-7.24 (2H, m, ArH), 7.22-7.16 (1H, m, ArH), 7.11-7.05 (2H, m, ArH), 6.96-6.90 (2H, m, ArH), 2.97 (1H, dd, $J = 13.2, 6.3$ Hz, ArCH₂), 2.88 (1H, dd, $J = 13.2, 8.3$ Hz, ArCH₂), 2.85-2.76 (1H, m, ArCH₂CH), 2.53 (3H, s, ArCH₃), 1.73-1.64 (2H, m, CH₂CH₂CH₂CH₃), 1.37-1.09 (4H, m, CH₂CH₂CH₃), 0.84 (3H, t, $J = 7.2$ Hz, CH₂CH₃); ^{13}C NMR (125.8 MHz, CDCl_3) δ 147.0 (C), 146.9 (C), 144.1 (C), 133.5 (C), 133.4 (CH), 128.3 (2 x CH), 127.6 (2 x CH), 127.4 (CH), 126.3 (CH), 124.6 (CH), 47.7 (CH), 43.4 (CH₂), 35.5 (CH₂), 29.7 (CH₂), 22.6 (CH₂), 20.7 (CH₃), 13.9 (CH₃); HRMS (ASAP) Exact mass calcd for $\text{C}_{19}\text{H}_{24}\text{N}_1\text{O}_2$ $[\text{M}+\text{H}]^+$: 298.1802, found: 298.1800. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); t_{r} (major) = 7.2 min, t_{r} (minor) = 8.1 min; 87% ee.



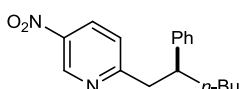
1-[(*S*)-2,4-diphenylbutyl]-4-nitronaphthalene (83r**)**. The title compound was prepared according to the General Procedure A from

alkenylarene **82x** (61 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (41 mg, 54%). $[\alpha]_D^{24} +55.9$ (*c* 1.36, CHCl₃); IR (film) 3026, 2927, 2856, 1736, 1514 (N-O), 1454, 1338 (N-O), 1219, 769, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.59 (1H, d, *J* = 8.6 Hz, ArH), 8.06 (1H, d, *J* = 8.5 Hz, ArH), 7.98 (1H, d, *J* = 7.8 Hz, ArH), 7.74-7.67 (1H, m, ArH), 7.64-7.58 (1H, m, ArH), 7.32-7.22 (5H, m, ArH), 7.20-7.17 (1H, m, ArH), 7.13-7.05 (5H, m, ArH), 3.50 (1H, dd, *J* = 13.8, 6.7 Hz, ArCH₂CH), 3.34 (1H, dd, *J* = 13.8, 7.9 Hz, ArCH₂CH), 3.10-2.99 (1H, m, ArCH₂CH), 2.58-2.39 (2H, m, CH₂Ph), 2.17-2.08 (2H, m, CH₂CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 145.5 (C), 144.3 (C), 143.8 (C), 141.8 (C), 132.6 (C), 128.7 (CH), 128.6 (2 x CH), 128.33 (2 x CH), 128.27 (2 x CH), 127.6 (2 x CH), 127.1 (CH), 126.7 (CH), 125.8 (CH), 125.7 (CH), 125.5 (C), 124.4 (CH), 123.8 (CH), 123.3 (CH), 46.5 (CH), 41.7 (CH₂), 37.7 (CH₂), 33.7 (CH₂); HRMS (ASAP) Exact mass calcd for C₂₆H₂₄N₁O₂ [M+H]⁺: 382.1802, found: 382.1802. Enantiomeric excess was determined by HPLC with a Chiralcel IB-3 column (99:1 hexane:isopropanol, 0.8 mL/min, 210 nm, -2.5 °C); t_r (minor) = 15.1 min, t_r (major) = 15.6 min; 84% ee.

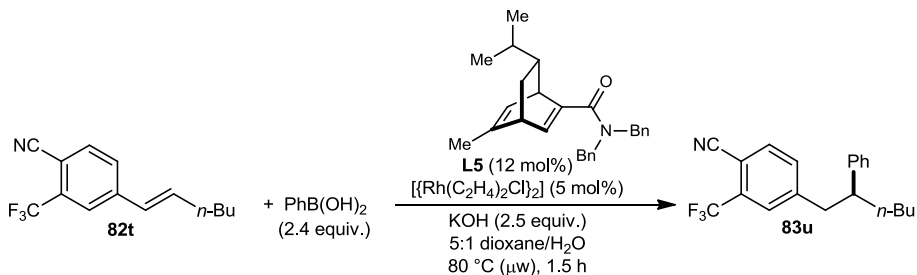


1-[(S)-2,4-Diphenylbutyl]-2-fluoro-4-nitrobenzene (83s). The title compound was prepared according to the General Procedure A from alkenylarene **82w** (54 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (63 mg, 90%). $[\alpha]_D^{24} +75.9$ (*c* 0.90, CHCl₃); IR (film) 3028, 2927, 1639, 1525 (N-O), 1493, 1350 (N-O), 1230, 1072, 741, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.86-7.80 (2H, m, ArH), 7.34-7.17 (6H, m, ArH), 7.16-7.08 (4H, m, ArH), 7.04-6.98 (1H, m, ArH), 3.22-3.11 (1H, m, ArCH₂), 3.00-2.90 (2H, m, ArCH₂CH), 2.60-2.45 (2H, m, CH₂CH₂Ph), 2.15-2.02 (2H, m, CH₂CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 160.3 (C, d, *J* = 249.6 Hz), 147.0 (C, d, *J* = 8.9 Hz), 143.0 (C), 141.8 (C), 135.5 (C, d, *J* = 16.2 Hz), 131.8 (CH, d, *J* = 5.4 Hz), 128.5 (2 x CH), 128.3 (2 x CH), 128.3 (2 x CH), 127.6 (2 x CH), 126.7 (CH), 125.8 (CH), 118.7 (CH, d, *J* = 3.5 Hz), 110.9 (CH, d, *J* = 27.9 Hz), 45.9 (CH), 37.5 (CH₂), 36.8 (CH₂), 33.6 (CH₂); ¹⁹F NMR (376 MHz, CDCl₃) δ -114.1 (1F, t, *J* = 8.3 Hz); HRMS (ASAP) Exact mass calcd for C₂₂H₂₁F₁N₁O₂ [M+H]⁺:

350.1551, found: 350.1549. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 27.1 min, t_r (major) = 32.9 min; 88% ee.

 **5-Nitro-2-[(S)-2-phenylhexyl]pyridine (83t).** The title compound was prepared according to the General Procedure A from alkenylpyridine **82v** (41 mg, 0.20 mmol) and phenylboronic acid (59 mg, 0.48 mmol) and purified by column chromatography (5% CH₂Cl₂/hexane→20% CH₂Cl₂/hexane) to give a yellow oil (52 mg, 91%). $[\alpha]_D^{24} +125.1$ (*c* 0.90, CHCl₃); IR (film) 2956, 2927, 2858, 1645, 1599, 1577, 1522 (N-O), 1468, 1350 (N-O), 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.33 (1H, d, *J* = 2.6 Hz, ArH), 8.19 (1H, dd, *J* = 8.5 Hz, 2.7 Hz, ArH), 7.26-7.20 (2H, m, ArH), 7.19-7.12 (1H, m, ArH), 7.10-7.05 (2H, m, ArH), 6.96 (1H, d, *J* = 8.5 Hz, ArH), 3.32-3.21 (1H, m, ArCH₂), 3.18-3.05 (2H, m, ArCH₂CH), 1.78-1.67 (2H, m, CH₂CH₂CH₂CH₃), 1.37-1.08 (4H, m, CH₂CH₂CH₃), 0.83 (3H, t, *J* = 7.2 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 167.7 (C), 144.6 (CH), 143.8 (C), 142.4 (C), 130.7 (CH), 128.4 (2 x CH), 127.5 (2 x CH), 126.4 (CH), 123.6 (CH), 46.4 (CH), 46.0 (CH₂), 36.0 (CH₂), 29.6 (CH₂), 22.6 (CH₂), 13.9 (CH₃); HRMS (ASAP) Exact mass calcd for C₁₇H₂₀N₂O₂ [M]⁺: 284.1530, found: 284.1522. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 13.1 min, t_r (major) = 19.7 min; 91% ee.

4-[(S)-2-Phenylhexyl]-2-trifluoromethylbenzonitrile (83u)

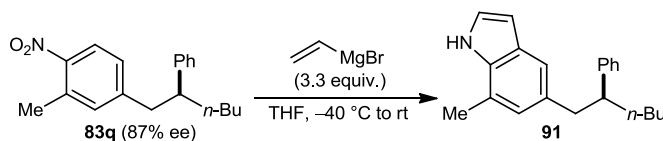


A solution of [Rh(C₂H₄)₂Cl]₂ (3.8 mg, 0.010 mmol) and ligand **L5** (9.2 mg, 0.024 mmol) in dioxane (0.3 mL) was stirred under nitrogen at room temperature for 15 min. This solution was then added *via* cannula to a sealed nitrogen-flushed microwave vial

containing alkenylarene **82t** (51 mg, 0.20 mmol), phenylboronic acid (59 mg, 0.48 mmol), KOH (28 mg, 0.50 mmol), and H₂O (0.1 mL), using further dioxane (0.2 mL) as a rinse. The resulting mixture was irradiated in a microwave reactor at 80 °C for 1.5 h. After cooling to room temperature, the mixture was filtered through a short plug of SiO₂ using CH₂Cl₂ as eluent and concentrated *in vacuo*. Purification of the residue twice by column chromatography (5% CH₂Cl₂/hexane) gave the *arylation product* **83u** (39 mg, 59%) as a colorless oil. $[\alpha]_D^{24} +58.9$ (*c* 1.39, CHCl₃); IR (film) 2931, 2860, 2231 (C≡N), 1606, 1496, 1321, 1178, 1138, 1057, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.61 (1H, d, *J* = 7.9 Hz, ArH), 7.32 (1H, s, ArH), 7.27-7.23 (2H, m, ArH), 7.22-7.16 (2H, m, ArH), 7.04-6.98 (2H, m, ArH), 3.07 (1H, dd, *J* = 13.4, 5.8 Hz, ArCH₂), 2.93 (1H, dd, *J* = 13.4, 9.2 Hz, ArCH₂), 2.83-2.74 (1H, m, ArCH₂CH), 1.77-1.66 (2H, m, CH₂CH₂CH₂CH₃), 1.39-1.09 (4H, m, CH₂CH₂CH₃), 0.84 (3H, t, *J* = 7.2 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 147.1 (C), 143.2 (C), 134.3 (CH), 132.7 (CH), 132.3 (C, d, *J* = 32.4 Hz), 128.5 (2 x CH), 127.6 (2 x CH), 127.4 (CH, q, *J* = 4.6 Hz), 126.6 (CH), 122.4 (C, q, *J* = 273.8 Hz), 115.7 (C), 107.3 (C, q, *J* = 2.2 Hz), 47.8 (CH), 43.8 (CH₂), 35.6 (CH₂), 29.6 (CH₂), 22.6 (CH₂), 13.9 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.4 (3F, s); HRMS (ASAP) Exact mass calcd for C₂₀H₂₁N₁F₃ [M+H]⁺: 332.1621, found: 332.1624. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); *t*_r (major) = 8.1 min, *t*_r (minor) 9.2 min; 84% ee.

Preparation of Indole 91

7-Methyl-5-[(*S*)-2-phenylhexyl]-1*H*-indole (**91**)

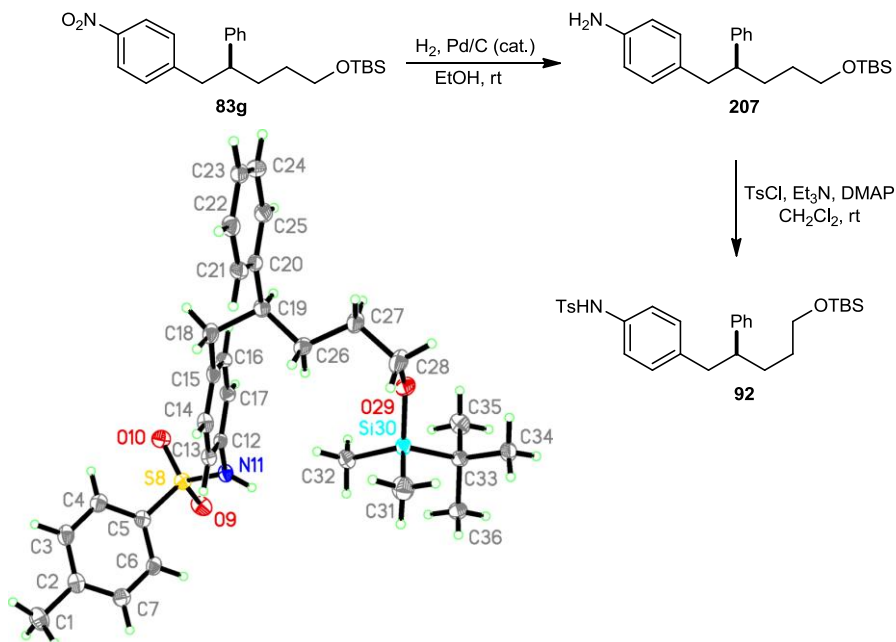


To a solution of nitroarene **83q** (119 mg, 0.40 mmol) in THF (4 mL) at -40 °C was added vinylmagnesium bromide (1 M in THF, 1.32 mL, 1.32 mmol) over 1 min and the resulting mixture was stirred at -40 °C for 2 h. The reaction was warmed to room temperature and quenched carefully with saturated aqueous NH₄Cl solution (20 mL). The

aqueous layer was extracted with Et₂O (3 x 40 mL) and the combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% CH₂Cl₂/hexane) gave the *indole* **91** (78 mg, 67%) as a pale yellow gum. $[\alpha]_D^{24} +57.6$ (*c* 1.25, CHCl₃); IR (film) 3419 (N-H), 2925, 2856, 1597, 1452, 1344, 1111, 760, 725, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.97 (1H, br s, NH), 7.33-7.24 (2H, m, ArH), 7.23-7.14 (5H, m, ArH), 6.74 (1H, br s, NCH=CH), 6.48 (1H, dd, *J* = 3.2, 2.0 Hz, NCH=CH), 3.04-2.79 (3H, m, ArCH₂CH), 2.45 (3H, s, ArCH₃), 1.79-1.52 (2H, m, CH₂CH₂CH₂CH₃), 1.32-1.05 (4H, m, CH₂CH₂CH₃), 0.79 (3H, t, *J* = 7.2 Hz, CH₂CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 146.2 (C), 134.0 (C), 132.5 (C), 128.1 (2 x CH), 127.8 (2 x CH), 127.3 (C), 125.7 (CH), 124.4 (CH), 123.7 (CH), 119.5 (C), 118.4 (CH), 102.8 (CH), 48.4 (CH), 44.0 (CH₂), 35.0 (CH₂), 29.8 (CH₂), 22.8 (CH₂), 16.7 (CH₃), 14.0 (CH₃); HRMS (ES) Exact mass calcd for C₂₁H₂₆N₁ [M+H]⁺: 292.2060 found: 292.2061.

Determination of Absolute Configurations

N-{4-[(*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-phenylpentyl]phenyl}-4-methylbenzenesulfonamide (**92**)



A solution of nitroarene **83g** (400 mg, 1.00 mmol) and 10% Pd/C (100 mg) in EtOH (20 mL) at room temperature was stirred under an atmosphere of hydrogen (balloon) for 3 h. The solution was filtered through a short plug of celite using CH₂Cl₂ as eluent (50 mL) and concentrated *in vacuo* to leave the amine **207**, which was used immediately without further purification. To the amine **207** was added a solution of TsCl (210 mg, 1.10 mmol), Et₃N (153 μ L, 1.10 mmol), and DMAP (147 mg, 1.20 mmol) in CH₂Cl₂ (7.5 mL) *via* cannula and the resulting solution was stirred at room temperature for 16 h. The reaction was concentrated *in vacuo* and the residue was purified by column chromatography (20% CH₂Cl₂/hexane \rightarrow 40 % CH₂Cl₂/hexane) to give the *sulfonamide* **92** (477 mg, 91%) as an off-white solid. Slow diffusion of hexane into a solution of **92** in EtOAc provided crystals that were suitable for X-ray crystallography. m.p. 84-86 $^{\circ}$ C; $[\alpha]_{\text{D}}^{24}$ +45.2 (*c* 1.06, CHCl₃); IR (film) 3255 (NH), 2927, 1512, 1462, 1394, 1336, 1161, 1093, 835, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.65 (2H, d, *J* = 8.3 Hz, ArH), 7.26-7.13 (5H, m, ArH), 7.07-7.01 (2H, m, ArH), 6.93 (2H, d, *J* = 8.5 Hz, ArH), 6.86 (2H, d, *J* = 8.5 Hz, ArH), 3.53 (2H, t, *J* = 6.5 Hz, CH₂O), 2.90-2.69 (3H, m, ArCH₂CH), 2.39 (3H, s, ArCH₃), 1.78-1.71 (1H, m, CH₂CH₂O), 1.66-1.60 (1H, m, CH₂CH₂O), 1.42-1.34 (2H, m, CH₂CH₂CH₂O), 0.88 (9H, s, C(CH₃)₃), 0.02 (3H, s, SiCH₃), 0.01 (3H, s, SiCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 144.5 (C), 143.5 (C), 137.9 (C), 136.0 (C), 134.1 (C), 129.8 (2 x CH), 129.4 (2 x CH), 128.1 (2 x CH), 127.7 (2 x CH), 127.2 (2 x CH), 126.0 (CH), 121.7 (2 x CH), 63.0 (CH₂), 47.7 (CH), 43.2 (CH₂), 31.6 (CH₂), 30.7 (CH₂), 25.9 (3 x CH₃), 21.5 (CH₃), 18.2 (C), -5.4 (2 x CH₃); HRMS (ES) Exact mass calcd for C₃₀H₄₂N₁O₃Si₁ [M+H]: 524.2649 found: 524.2638.

The sense of enantioinduction observed using ligand **L5** is consistent with reported examples of arylation of acyclic electron-deficient alkenes using structurally similar chiral dienes,^{43, 92} and the absolute configurations of the remaining arylation products in this study were assigned by analogy with that of **83g**.

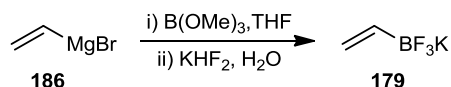
Chapter II: Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes with Ketones

General Information

THF and toluene were dried and purified by passage through activated alumina columns using a solvent purification system. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilen 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using vanillin, potassium permanganate, or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.¹⁹⁴ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker AV500 (500 MHz), a Bruker AVA400 (400 MHz) spectrometer, or a Bruker OPEN400 (400 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker AV500 (125.8 MHz) spectrometer or a Bruker AVA400 (100.6 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ¹⁹F NMR spectra were recorded on a Bruker AVA 400 MHz (376 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield of CFCl₃, using fluorobenzene as internal standard (C₆H₅F at -113.2 ppm). High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or

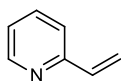
on a Finnigan MAT 900 XLT spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Chiral HPLC analysis was performed on an Agilent 1100 instrument using 4.6 x 250 mm columns. Authentic racemic samples of products for chiral HPLC assay determinations were obtained using *rac*-BINAP as the ligand.

Preparation of Potassium Vinyltrifluoroborate (**179**)¹⁸⁹



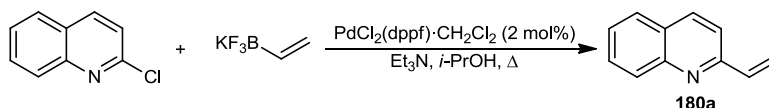
To a solution of trimethyl borate (6.9 mL, 62 mmol) in THF (45 mL) was added dropwise vinylmagnesium bromide **186** (1.0 M THF solution, 50 mL, 50 mmol) at $-78\text{ }^\circ\text{C}$. The resulting suspension was stirred for 20 min at $-78\text{ }^\circ\text{C}$ and then allowed to warm to rt for 1 h. The mixture was then cooled to $0\text{ }^\circ\text{C}$ and KHF₂ (19 g, 248 mmol) was added followed by the addition of water (35 mL) over 30 min. After stirring at rt for 20 min, the solution was concentrated and the crude material was dissolved in acetone, filtered and concentrated. The resulting white solid was purified by dissolving in hot acetone and precipitating with Et₂O, to give **179** (3.5 g, 95%) as a white solid that displayed spectroscopic data consistent with those reported previously.¹⁸⁹

Preparation of Alkenylazaarenes



2-Vinylpyridine (180b). Commercially available.

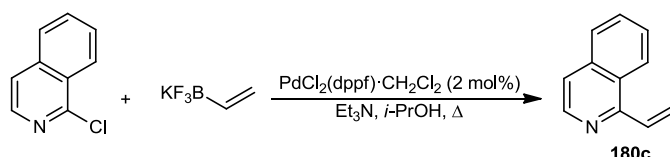
2-Vinylquinoline (**180a**)¹⁹⁸



A solution of 2-chloroquinoline (1.64 g, 10.0 mmol), potassium vinyltrifluoroborate (1.61 g, 12.0 mmol), PdCl₂(dppf)·CH₂Cl₂ (163 mg, 0.20 mmol), and Et₃N (1.39 mL, 10.0

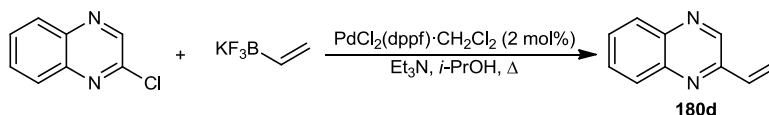
mmol) in *i*-PrOH (156 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave 2-vinylquinoline (**180a**) (1.26 g, 81%) as a pale yellow oil that displayed spectroscopic data consistent with those reported previously.¹⁹⁸

1-Vinylisoquinoline (**180c**)¹⁹⁹



A solution of 1-chloroisoquinoline (2.62 g, 16.0 mmol), potassium vinyltrifluoroborate (2.57 g, 19.2 mmol), PdCl₂(dppf)·CH₂Cl₂ (261 mg, 0.32 mmol), and Et₃N (2.23 mL, 16.0 mmol) in *i*-PrOH (160 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (80 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 100 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) gave 1-vinylisoquinoline (**180c**) (1.41 g, 57%) as a dark brown oil that displayed spectroscopic data consistent with those reported previously.¹⁹⁹

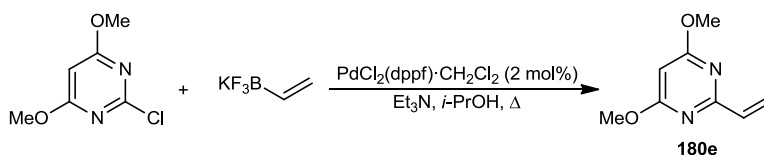
2-Vinylquinoxaline (**180d**)²⁰⁰



A solution of 2-chloroquinoxaline (1.32 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The

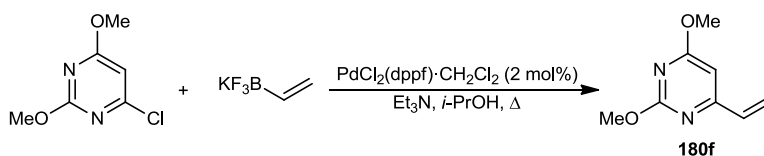
aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylquinoxaline* **180d** (944 mg, 76%) as an orange oil that displayed spectroscopic data consistent with those reported previously.²⁰⁰

2-Vinyl-4,6-dimethoxypyrimidine (180e)



A solution of 2-chloro-4,6-methoxypyrimidine (1.40 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylpyrimidine* **180e** (1.00 g, 75%) as a pale yellow oil. IR (film) 2953, 1583, 1396, 1378, 1261, 1191, 1164, 1043, 987, 830 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.70 (1H, dd, *J* = 17.3, 10.2 Hz, CH=CH₂), 6.60 (1H, dd, *J* = 17.3, 2.2 Hz, CH=CH₂), 5.92 (1H, s, ArH), 5.68 (1H, dd, *J* = 10.2, 2.2 Hz, CH=CH₂), 3.97 (6H, s, 2 x OCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.3 (2 x C), 163.3 (C), 136.5 (CH), 123.6 (CH₂), 88.0 (CH), 53.9 (2 x CH₃); HRMS (ESI) Exact mass calcd for C₈H₁₁N₂O₂ [M+H]⁺: 167.0815, found:167.014.

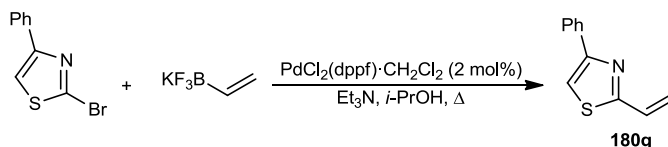
4-Vinyl-2,6-dimethoxypyrimidine (180f)



A solution of 6-chloro-2,4-methoxypyrimidine (1.40 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and

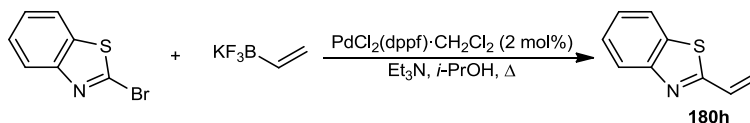
Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylpyrimidine* **180f** (1.07 g, 80%) as a pale yellow oil. IR (film) 2954, 1557, 1456, 1337, 1204, 1106, 1031, 840, 791, 598 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.60 (1H, dd, *J* = 17.2, 10.4 Hz, CH=CH₂), 6.46 (1H, dd, *J* = 17.2, 1.7 Hz, CH=CH₂), 6.29 (1H, s, ArH), 5.58 (1H, dd, *J* = 10.4, 1.7 Hz, CH=CH₂), 4.02 (3H, s, OCH₃), 3.98 (3H, s, OCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.4 (C), 165.3 (C), 164.1 (C), 134.7 (CH), 121.9 (CH₂), 99.3 (CH), 54.6 (CH₃), 53.9 (CH₃); HRMS (ESI) Exact mass calcd for C₈H₁₁N₂O₂ [M+H]⁺: 167.0815, found:167.0814.

2-Vinyl-4-phenyl-1,3-thiazole (180g)



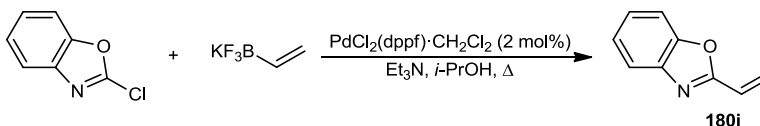
A solution of 2-bromo-4-phenylthiazole (1.92 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *vinylthiazole* **180g** (1.40 g, 93%) as a green solid. m.p. 28-30 °C; IR (film) 3111, 1602, 1485, 1443, 1079, 978, 919, 852, 737, 705 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.94-7.89 (2H, m, ArH), 7.46-7.41 (2H, m, ArH), 7.40 (1H, s, ArH), 7.37-7.33 (1H, m, ArH), 7.00 (1H, ddd, *J* = 17.5, 10.9, 0.5 Hz, CH=CH₂), 6.11 (1H, dd, *J* = 17.5 Hz, CH=CH₂), 5.59 (1H, dd, *J* = 10.9 Hz, CH=CH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 166.9 (C), 156.0 (C), 134.3 (C), 130.6 (CH), 128.7 (2 x CH), 128.2 (CH), 126.4 (2 x CH), 119.9 (CH₂), 112.3 (CH); *m/z* (EI) 187 ([M]⁺, 100).

2-Vinyl-1,3-benzothiazole (**180h**)



A solution of 2-bromobenzothiazole (1.00 g, 4.67 mmol), potassium vinyltrifluoroborate (0.75 g, 5.61 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (76 mg, 0.09 mmol), and Et_3N (0.65 mL, 4.67 mmol) in $i\text{-PrOH}$ (60 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the vinylbenzothiazole **180h** (0.530 g, 70%) as a pale yellow solid. IR (film) 3060, 2359, 1489, 1437, 1312, 1108, 984, 927, 758, 728 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.00 (1H, m, ArH), 7.86 (1H, ddd, $J = 7.9, 1.1, 0.6$ Hz, ArH), 7.48 (1H, ddd, $J = 8.3, 7.3, 1.2$ Hz, ArH), 7.39 (1H, ddd, $J = 8.3, 7.3, 1.2$ Hz, ArH), 7.06 (1H, dd, $J = 17.5, 10.9$ Hz, CH=CH₂), 6.20 (1H, d, $J = 17.5$ Hz, CH=CH₂), 5.78 (1H, d, $J = 10.9$ Hz, CH=CH₂); ^{13}C NMR ((125.8 MHz, CDCl_3) δ 167.2 (C), 153.6 (C), 134.3 (C), 131.4 (CH), 126.3 (CH), 125.6 (CH), 123.3 (CH), 123.2 (CH₂), 121.6 (CH); m/z (ES) 161.1 ($[\text{M}+\text{H}]^+$, 100).

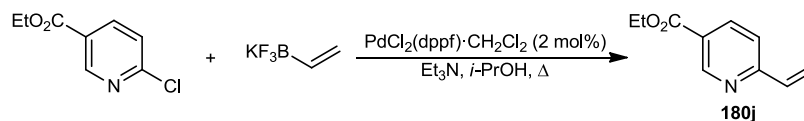
2-Vinyl-1,3-benzoxazole (**180i**)²⁰¹



A solution of 2-chlorobenzoxazole (768 mg, 5.0 mmol), potassium vinyltrifluoroborate (800 mg, 6.0 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (82 mg, 0.082 mmol), and Et_3N (0.7 mL, 5.0 mmol) in $i\text{-PrOH}$ (80 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave

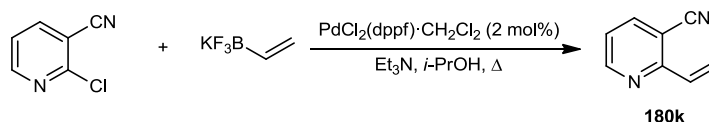
the *vinylbenzoxazole* **180i** (726 mg, 67%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.²⁰¹

Ethyl 6-vinylpyridine-3-carboxylate (**180j**)



A solution of ethyl-6-chloronicotinate (1.48 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylpyridine* **180j** (1.30 g, 92%) as a pale orange oil. IR (film) 2938, 1722 (C=O), 1595, 1368, 1287, 1115, 1025, 856, 800, 741 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.17 (1H, d, *J* = 1.8 Hz, ArH), 8.25 (1H, dd, *J* = 8.2, 2.2 Hz, ArH), 7.40 (1H, d, *J* = 8.2 Hz, ArH), 6.87 (1H, dd, *J* = 17.5, 10.8 Hz, CH=CH₂), 6.34 (1H, dd, *J* = 17.5, 1.0 Hz, CH=CH₂), 5.62 (1H, dd, *J* = 10.8, 1.0 Hz, CH=CH₂), 4.41 (2H, q, *J* = 7.1 Hz, OCH₂CH₃), 1.41 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 165.2 (C), 159.1 (C), 150.8 (CH), 137.6 (CH), 136.2 (CH), 124.8 (C), 120.9 (CH₂), 120.6 (CH), 61.3 (CH₂), 14.3 (CH₃); *m/z* (EI) 177 ([M]⁺, 100).

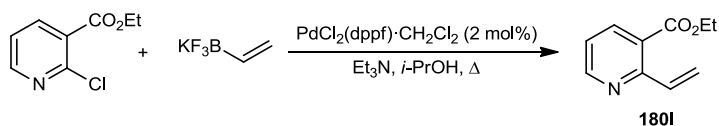
2-Vinyl-nicotinitrile (**180k**)



A solution of 2-chloronicotinonitrile (1.11 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The

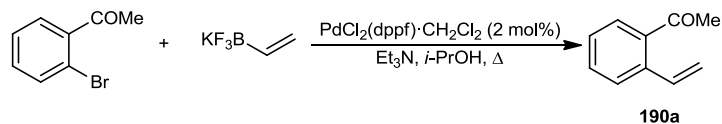
aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylnicotinitrile* **180k** (847 mg, 81%) as a pink solid. IR (film) 3048, 2227 (C≡N), 1577, 1553, 1442, 1393, 1098, 982, 947, 795 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.77 (1H, dd, *J* = 4.8, 1.7 Hz, ArH), 7.93 (1H, dd, *J* = 7.9, 1.8 Hz, ArH), 7.29 (1H, dd, *J* = 7.9, 4.8 Hz, ArH), 7.20 (1H, dd, *J* = 16.9, 10.7 Hz, ArCH=CH), 6.67 (1H, dd, *J* = 16.9, 1.9 Hz, ArCH=CH₂), 5.76 (1H, dd, *J* = 10.7, 1.5 Hz, ArCH=CH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 157.1(C), 152.7 (CH), 140.4 (CH), 132.0 (CH), 123.9 (CH₂), 122.0 (CH), 116.4 (C), 107.6 (C); *m/z* (ES) 130.1 ([M+H]⁺, 100).

Ethyl-2-vinyl-nicotinate (**180l**)



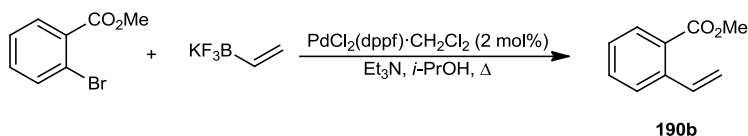
A solution of ethyl-2-chloronicotinate (928 mg, 5.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylnicotinate* **180l** (804 mg, 91%) as a dark yellow oil. IR (film) 2982, 1722 (C=O), 1581, 1557, 1437, 1263, 1140, 1073, 990, 940, 797, 743 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.69 (1H, dd, *J* = 4.7, 1.8 Hz, ArH), 8.15 (1H, dd, *J* = 7.9, 1.8 Hz, ArH), 7.62 (1H, dd, *J* = 17.0, 10.7 Hz, ArH), 7.23 (1H, dd, *J* = 7.9, 4.7 Hz, ArH), 6.49 (1H, dd, *J* = 17.0, 2.2 Hz, ArCH=CH), 5.59 (1H, dd, *J* = 10.7, 2.2 Hz, ArCH=CH), 4.39 (2H, q, *J* = 7.14, 7.12 Hz, -OCH₂CH₃), 1.4 (3H, t, *J* = 7.14 Hz, -OCH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 166.4(C), 155.0 (C), 151.9 (CH), 138.4 (CH), 133.8 (CH), 124.6 (C), 121.8 (CH), 121.4 (CH₂), 61.5 (CH₂), 14.2 (CH₃); *m/z* (ES) 177.1 ([M+H]⁺, 100).

2-Vinylacetophenone (**190a**)²⁰²



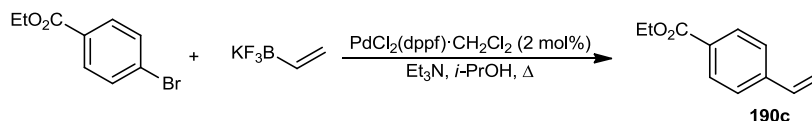
A solution of 2-bromoacetophenone (0.40 mL, 3.00 mmol), potassium vinyltrifluoroborate (482 mg, 3.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (49 mg, 0.06 mmol), and Et_3N (0.42 mL, 3.00 mmol) in $i\text{-PrOH}$ (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylacetophenone* **190a** (847 mg, 81%) as a colourless oil that displayed spectroscopic data consistent with those reported previously.²⁰²

1-(1-Methoxy)-2-vinylbenzene (**190b**)²⁰³

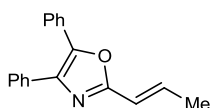


A solution of methyl 2-bromobenzoate (1.12 mL, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (131 mg, 0.16 mmol), and Et_3N (1.12 mL, 8.00 mmol) in $i\text{-PrOH}$ (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylbenzene* **190b** (1.10 g, 85%) as a clear colourless oil that displayed spectroscopic data consistent with those reported previously.²⁰³

Ethyl-4-ethenylbenzoate (**190c**)²⁰⁴

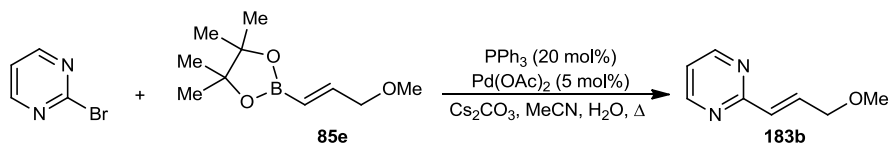


A solution of ethyl-4-bromobenzoate (1.31 mL, 3.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.16 mmol), and Et₃N (1.12 mL, 8.00 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (50 mL) and H₂O (20 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 20 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *ethenylbenzoate* **190c** (1.13 g, 80%) as a clear colourless oil that displayed spectroscopic data consistent with those reported previously.²⁰⁴



(E)-4,5-Diphenyl-2-(prop-1-en-1-yl)oxazole (183a). Prepared by other members of our group according to a previously reported procedure.²⁰⁵

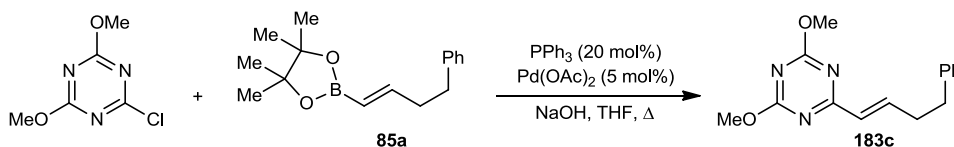
2-[(E)-3-Methoxyprop-1-en-1-yl]pyrimidine (183b)



A solution of 2-bromopyrimidine (477 mg, 3.00 mmol), alkenylboronic ester **85e** (588 μ L, 2.77 mmol), Pd(OAc)₂ (34 mg, 0.15 mmol), PPh₃ (157 mg, 0.60 mmol), and Cs₂CO₃ (1.95 g, 6.00 mmol) in MeCN (30 mL) and H₂O (8 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, diluted with H₂O (30 mL), and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane→40% EtOAc/hexane) gave the *alkenylpyrimidine* **183b** (303 mg, 75%) as a yellow oil. IR (film) 1723, 1659, 1557, 1420, 1383, 1319, 1192, 1122, 977, 749 cm⁻¹; ¹H NMR (500

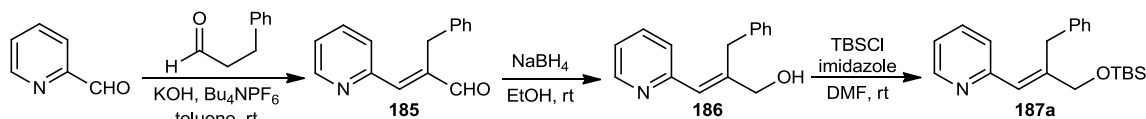
MHz, CDCl₃) 8.69 (2H, d, J = 4.7 Hz, ArH), 7.19 (1H, dt, J = 15.7, 5.7 Hz, =CHCH₂), 7.12 (1H, t, J = 4.9 Hz, ArH), 6.83-6.76 (1H, m, CH=CHCH₂), 4.21 (2H, dd, J = 5.2, 1.7 Hz, CH₂), 3.44 (3H, s, OCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 164.2 (C), 157.0 (2 x CH), 137.1 (CH), 130.4 (CH), 118.8 (CH), 72.1 (CH₂), 58.4 (CH₃); HRMS (EI) Exact mass calcd for C₈H₁₀N₂O₁ [M]⁺: 150.0788, found: 150.0787.

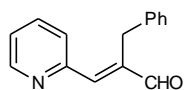
2,4-Dimethoxy-6-[(*E*)-3-methoxyprop-1-en-1-yl]-1,3,5-triazine (183c)



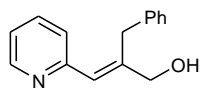
A solution of 2-chloro-4,6-dimethyl-1,3,5-triazine (1.40 g, 8.00 mmol), boronic ester **85a**¹⁹⁵ (2.27 g, 8.80 mmol), Pd(OAc)₂ (269 mg, 1.20 mmol), PPh₃ (630 mg, 2.40 mmol), and NaOH (960 mg, 24.0 mmol) in THF (80 mL) was heated to reflux for 2 h. The mixture was cooled to room temperature, diluted with H₂O (60 mL), and extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave the *alkenyltriazine* **183c** (1.41g, 65%) as a pale brown solid. m.p. 52-54 °C; IR (film) 1654, 1559, 1498, 1458, 1352, 1201, 1111, 1082, 979, 816 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.48 (1H, dt, J = 15.6, 6.9 Hz, =CHCH₂), 7.33-7.28 (2H, m, ArH), 7.24-7.18 (3H, m, ArCH), 6.39 (1H, d, J = 15.6 Hz, CH=CHCH₂), 4.05 (6H, s, 2 x OCH₃), 2.88-2.81 (2H, m, CH₂Ph), 2.68-2.60 (2H, m, CH₂CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 174.6 (C), 172.5 (C), 146.3 (CH), 141.0 (C), 128.5 (2 x CH), 128.3 (2 x CH), 126.1 (CH), 55.0 (2 x CH₃), 34.6 (CH₂), 34.4 (CH₂); HRMS (EI) Exact mass calcd for C₁₅H₁₈N₃O₂ [M]⁺: 272.1394, found: 272.1391.

Preparation of Alkene 187a





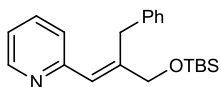
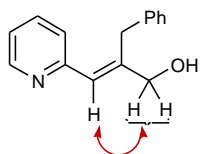
(Z)-2-Benzyl-3-pyridin-2-ylpropenal (185). Following a slight modification of a literature procedure for a similar compound,²⁰⁶ to a vigorously stirred suspension of Bu₄NPF₆ (387 mg, 1.00 mmol) and KOH (84 mg, 1.50 mmol) in toluene (15 mL) was added 2-pyridinecarboxaldehyde (0.95 mL, 10.0 mmol) dropwise over 1 min, followed by hydrocinnamaldehyde (1.76 mL, 12.0 mmol) dropwise over 2 min. The reaction was stirred vigorously at room temperature for 5 h, and then partitioned between H₂O (50 mL) and CH₂Cl₂ (50 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane→60% EtOAc/hexane) gave the *enal* **185** (819 mg, 37%) as a red-brown solid. m.p. 46-48 °C; IR (CHCl₃) 3059, 2924, 2823, 2717, 2360, 1684 (C=O), 1631 (C=C), 1579, 1308, 1136, 739; ¹H NMR (250 MHz, CDCl₃) δ 9.53 (1H, s, CHO), 8.61-8.59 (1H, m, ArH), 7.57 (1H, dt, *J* = 7.8, 1.9 Hz, ArH), 7.29 (1H, d, *J* = 7.8 Hz, ArH), 7.21-6.98 (7H, m, ArH and CH=CCH₂Ph), 4.24 (2H, s, CH₂Ph); ¹³C NMR (62.9 MHz, CDCl₃) δ 195.3 (CH), 153.7 (C), 149.8 (CH), 147.6 (CH), 143.7 (C), 139.0 (C), 136.4 (CH), 128.6 (2 x CH), 128.1 (2 x CH), 126.2 (CH), 125.8 (CH), 123.7 (CH), 29.8 (CH₂); HRMS (ES) Exact mass calcd for C₁₅H₁₄N₁O₁ [M+H]⁺: 224.1070, found: 224.1065.



(Z)-2-Benzyl-3-pyridin-2-ylprop-2-en-1-ol (186). To a solution of aldehyde **185** (447 mg, 2.00 mmol) in EtOH (10 mL) at room temperature was added NaBH₄ (227 mg, 6.00 mmol) portionwise over 5 min. The resulting mixture was stirred at room temperature for 1 h and quenched carefully with saturated aqueous NH₄Cl solution (20 mL). Most of the EtOH was removed *in vacuo*, and the aqueous residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (50% EtOAc/hexane) gave the *alcohol* **186** (451 mg, 99%) as a cream solid. m.p. 67-69 °C; IR (film) 3273 (OH), 3025, 2906, 1659 (C=C), 1585, 1472, 1151, 1052, 733, 620 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.46-8.40 (1H, m, ArH), 7.49 (1H, dt, *J* = 7.7, 1.8 Hz, ArH), 7.16-7.03 (6H, m, ArH), 7.00 (1H, ddd, *J* = 7.5, 4.9, 0.9 Hz, ArH), 6.75 (1H, s, CH=CCH₂Ph), 4.04 (2H, d, *J* = 1.2 Hz, CH₂OH), 3.88 (2H, s,

CH_2Ph); ^{13}C NMR (62.9 MHz, CDCl_3) δ 156.3 (C), 148.8 (CH), 145.0 (C), 139.2 (C), 136.3 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 125.9 (CH), 124.3 (CH), 123.7 (CH), 121.3 (CH), 65.2 (CH_2), 34.2 (CH_2); HRMS (ES) Exact mass calcd for $\text{C}_{15}\text{H}_{16}\text{N}_1\text{O}_1$ $[\text{M}+\text{H}]^+$: 226.1226, found: 226.1223.

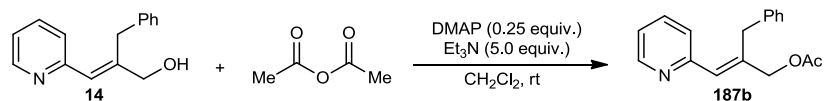
The stereochemistry of alcohol **186** was determined using an NOE experiment, which displayed the following diagnostic enhancement:



2-[(*E*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-3-phenylpropenyl]pyridine (187a**).**

To a solution of the alcohol **186** (0.50 mmol) and imidazole (85 mg, 1.25 mmol) in DMF (2 mL) at room temperature was added TBSCl (98 mg, 0.65 mmol) in one portion, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and the mixture was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with brine (15 mL). The brine layer was separated and extracted with Et_2O (2 x 20 mL), and the combined organic layers were dried (MgSO_4), and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc /hexane) gave the *alkenylpyridine* **187a** (134 mg, 79%) as a yellow oil. IR (film) 2927, 2855, 1691 ($\text{C}=\text{C}$), 1585, 1471, 1431, 1256, 1084, 836, 776 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.62-8.56 (1H, m, ArH), 7.63-7.55 (1H, m, ArH), 7.29-7.14 (6H, m, ArH), 7.12-7.05 (1H, m, ArH), 6.79 (1H, s, CCHC), 4.15 (2H, d, $J = 1.7$ Hz, OCH_2), 4.07 (2H, s, PhCH_2), 0.93 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.04 (6H, s, $\text{Si}(\text{CH}_3)_2$); ^{13}C NMR (90.6 MHz, CDCl_3) δ 156.7 (C), 149.2 (CH), 144.3 (C), 139.7 (C), 136.0 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 125.9 (CH), 124.1 (CH), 123.9 (CH), 121.1 (CH), 66.0 (CH_2), 34.1 (CH_2), 25.9 (3 x CH_3), 18.3 (C), -5.5 (2 x CH_3); m/z (ES) 340 ($[\text{M}+\text{H}]^+$, 100).

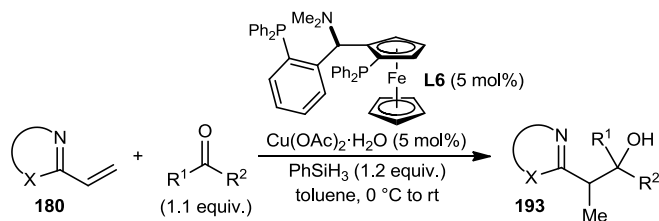
Acetic acid (*E*)-2-benzyl-3-pyridin-2-ylallyl ester (187b**)**



To a solution of the alcohol **186** (225 mg, 1.00 mmol), Et₃N (697 μ L, 5.00 mmol), and DMAP (31 mg, 0.25 mmol) in CH₂Cl₂ (5 mL) at room temperature was added acetic anhydride (198 μ L, 2.10 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous Na₂CO₃ solution (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane→50% EtOAc/hexane) gave the *acetic ester* **187b** (207 mg, 78%) as a pale yellow oil. IR (film) 3026, 1739 (C=O), 1658, 1584, 1494, 1431, 1372, 1227, 1029, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.72-8.50 (1H, m, ArH), 7.69-7.57 (1H, m, ArH), 7.33-7.07 (7H, m, ArH), 6.73 (1H, s, CCHC), 4.62 (2H, s, OCH₂), 4.16 (2H, s, PhCH₂), 2.04 (3H, s, CH₃); ¹³C NMR (90.6 MHz, CDCl₃) δ 170.4 (C), 155.5 (C), 149.1 (CH), 139.3 (C), 138.8 (C), 136.0 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 127.7 (CH), 126.0 (CH), 124.1 (CH), 121.6 (CH), 67.3 (CH₂), 34.5 (CH₂), 20.7 (CH₃); *m/z* (ES) 268 ([M+H]⁺, 100).

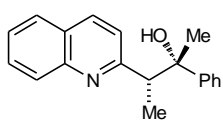
Copper-Catalyzed Reductive Coupling of Alkenylazaarenes with Ketones

General Procedure B: Reductive Coupling of Vinylazaarenes Using Ligand L13 (0.40 mmol Scale)

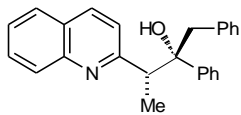


A solution of the appropriate vinylazaarene (0.40 mmol), Cu(OAc)₂·H₂O (4.0 mg, 0.02 mmol), ligand SL-T001-1 (**L13**) (13.8 mg, 0.02 mmol), and the appropriate ketone (0.44 mmol) in toluene (2 mL) was stirred at 0 °C for 15 min. PhSiH₃ (59 μ L, 0.48 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg),

and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give the reductive coupling product.



(2S,3R)-2-Phenyl-3-(quinolin-2-yl)butan-2-ol (193a). The title compound was prepared according to General Procedure B from 2-vinylquinoline **180a** (62 mg, 0.40 mmol) and acetophenone (51 μ L, 0.44 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (66 mg, 60%). m.p. 108-110 $^{\circ}$ C; $[\alpha]_D^{24} +14.2$ (*c* 0.84, CHCl_3); IR (film) 3312 (OH), 1598, 1558, 1504, 1456, 1412, 1065, 843, 762, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.17 (1H, d, *J* = 8.4 Hz, ArH), 8.08 (1H, d, *J* = 8.5 Hz, ArH), 7.84 (1H, d, *J* = 8.0 Hz, ArH), 7.77-7.73 (1H, m, ArH), 7.62 (2H, d, *J* = 7.4 Hz, ArH), 7.58-7.53 (1H, m, ArH), 7.41 (2H, t, *J* = 7.8 Hz, ArH), 7.36 (1H, d, *J* = 8.4 Hz, ArH), 7.30-7.26 (1H, m, ArH), 7.06 (1H, br s, OH), 3.36 (1H, q, *J* = 7.0 Hz, CHCH_3), 1.41 (3H, s, CH_3COH), 1.13 (3H, d, *J* = 7.1 Hz, CHCH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 166.1 (C), 147.4 (C), 146.9 (C), 137.1 (CH), 129.9 (CH), 128.8 (CH), 128.0 (2 x CH), 127.6 (CH), 126.9 (C), 126.22 (CH), 126.18 (CH), 125.0 (2 x CH), 122.5 (CH), 76.4 (C), 50.7 (CH), 30.8 (CH_3), 17.1 (CH_3); HRMS (ESI) Exact mass calcd for $\text{C}_{19}\text{H}_{20}\text{N}_1\text{O}_1$ $[\text{M}+\text{H}]^+$: 278.1539, found: 278.1541. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 $^{\circ}$ C); t_r (minor) = 12.6 min, t_r (major) = 20.3 min; 93% ee.

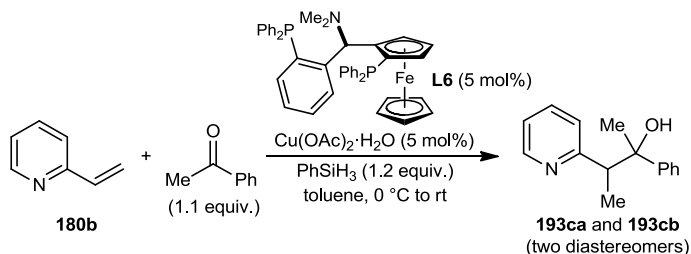


(2S,3R)-1,2-Diphenyl-3-(quinolin-2-yl)butan-2-ol (193b). The title compound was prepared according to General Procedure B from 2-vinylquinoline **180a** (62 mg, 0.40 mmol) and 2-phenylacetophenone (86 mg, 0.44 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (85 mg, 60%). m.p. 108-110 $^{\circ}$ C; $[\alpha]_D^{24} +55.2$ (*c* 1.05, CHCl_3); IR (film) 3302 (OH), 1599, 1504, 1452, 1424, 1327, 1074, 832, 754, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.22 (1H, d, *J* = 8.4 Hz, ArH), 8.13 (1H, d, *J* = 8.5 Hz, ArH), 7.87 (1H, d, *J* = 8.1 Hz, ArH), 7.78 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, ArH), 7.61-7.56 (1H, m, ArH),

7.47-7.40 (3H, m, ArH), 7.36-7.27 (3H, m, ArH and OH), 7.25-7.20 (1H, m, ArH), 7.02-6.98 (3H, m, ArH), 6.70 (2H, dd, $J = 6.4, 3.1$ Hz, ArH), 3.60 (1H, q, $J = 7.0$ Hz, CHCH₃), 3.10 (1H, d, $J = 13.4$ Hz, CH₂Ph), 2.90 (1H, d, $J = 13.4$ Hz, CH₂Ph), 1.17 (3H, d, $J = 7.1$ Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 166.2 (C), 146.8 (C), 144.5 (C), 137.5 (C), 137.3 (CH), 130.5 (2 x CH), 130.0 (CH), 128.7 (CH), 127.6 (4 x CH), 127.1 (2 x CH), 126.8 (C), 126.3 (CH), 126.1 (CH), 125.9 (CH), 125.6 (CH), 122.7 (CH), 79.6 (C), 49.0 (CH), 48.9 (CH₂), 17.5 (CH₃); HRMS (ESI) Exact mass calcd for C₂₅H₂₄N₁O₁ [M+H]⁺: 354.1852, found: 354.1856. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 10.9 min, t_r (minor) = 12.4 min; 97% ee.

Vapor diffusion of hexane into an EtOAc solution of **193b** gave crystals suitable for X-ray diffraction.

2-Phenyl-3-(pyridin-2-yl)butan-2-ol (**193ca** and **193cb**)

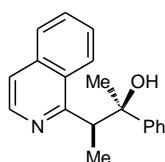


General Procedure B was followed using 2-vinylpyridine **180b** (43 μ L, 0.40 mmol) and acetophenone (51 μ L, 0.44 mmol). Purification by column chromatography (5% EtOAc/hexane) gave the *tertiary alcohol* **193cb** (28 mg, 31%) as a white solid followed by the *tertiary alcohol* **193ca** (59 mg, 65%) as a colorless oil.

Data for **193ca**: $[\alpha]_{\text{D}}^{24} +190.2$ (c 1.13, CHCl₃); IR (film) 3313 (OH), 2982, 1596, 1569, 1474, 1441, 1067, 933, 763, 701 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.40-8.35 (1H, m, ArH), 7.38 (1H, td, $J = 7.7, 1.8$ Hz, ArH), 7.35-7.30 (2H, m, ArH), 7.17-7.10 (2H, m, ArH), 7.04-7.01 (1H, m, ArH), 6.98 (1H, ddd, $J = 7.5, 4.9, 1.1$ Hz, ArH), 6.79-6.78 (1H, m, ArH), 6.61 (1H, br s, OH), 3.29 (1H, q, $J = 7.0$ Hz, CHCH₃), 1.57 (3H, s, CH₃COH), 1.47 (3H, d, $J = 7.0$ Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 164.8 (C), 149.4 (C), 147.9 (CH), 136.6 (CH), 127.5 (2 x CH), 125.7 (CH), 124.8 (2 x CH), 123.4 (CH), 121.2 (CH), 76.3 (C), 49.3 (CH), 27.8 (CH₃), 16.2 (CH₃); HRMS (ESI) Exact mass calcd for

C₁₅H₁₈N₁O₁ [M+H]⁺: 228.1383, found: 228.1385. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 19.7 min, t_r (minor) *ca.* 23 min (not detected); >99% ee.

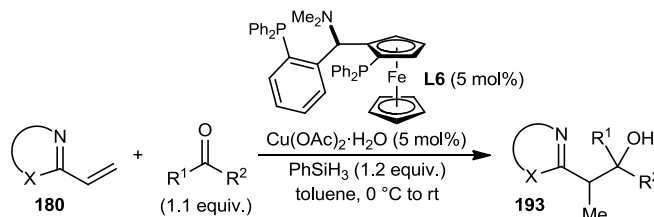
Data for **193cb**: m.p. 94-95 °C; [α]_D²⁴ +73.5 (*c* 1.06, CHCl₃); IR (film) 3329 (OH), 2972, 1596, 1472, 1407, 1364, 1066, 1017, 759, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.56 (1H, dd, *J* = 5.2, 2.0 Hz, ArH), 7.68 (1H, td, *J* = 7.7, 1.9 Hz, ArH), 7.59-7.54 (2H, m, ArH), 7.41-7.34 (2H, m, ArH), 7.28-7.19 (3H, m, ArH), 6.53 (1H, br s, OH), 3.16 (1H, q, *J* = 7.0 Hz, CHCH₃), 1.33 (3H, s, CH₃COH), 1.04 (3H, d, *J* = 7.1 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 165.1 (C), 148.4 (CH), 147.4 (C), 137.1 (CH), 127.9 (2 x CH), 126.1 (CH), 125.0 (2 x CH), 123.9 (CH), 121.6 (CH), 76.1 (C), 50.2 (CH), 30.7 (CH₃), 16.9 (CH₃); HRMS (ESI) Exact mass calcd for C₁₅H₁₈N₁O₁ [M+H]⁺: 228.1383, found: 228.1386. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 13.1 min, t_r (major) = 15.2 min; 92% ee.



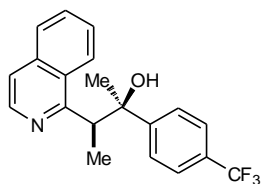
(2R,3S)-3-(Isoquinolin-1-yl)-2-phenylbutan-2-ol (193d). The title compound was prepared according to General Procedure B from 2-vinylisoquinoline **180c** (62 mg, 0.40 mmol) and acetophenone (51 μL, 0.44 mmol) and purified by column chromatography (5% EtOAc/hexane)

to give a white solid (84 mg, 76%). m.p 72-74 °C; [α]_D²⁴ -111.9 (*c* 0.97, CHCl₃); IR (film) 3290 (OH), 1561, 1502, 1457, 1385, 1065, 1002, 824, 768, 744 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.48 (1H, d, *J* = 5.7 Hz, ArH), 8.29 (1H, d, *J* = 8.5 Hz, ArH), 7.89 (1H, d, *J* = 8.1 Hz, ArH), 7.77-7.65 (4H, m, ArH), 7.61 (1H, d, *J* = 5.7 Hz, ArH), 7.49 (1H, br s, OH), 7.44 (2H, t, *J* = 7.8 Hz, ArH), 7.33-7.28 (1H, m, ArH), 4.12 (1H, q, *J* = 7.0 Hz, CHCH₃), 1.38 (3H, s, CH₃COH), 1.13 (3H, d, *J* = 7.0 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 165.8 (C), 147.8 (C), 140.4 (CH), 136.6 (C), 130.3 (CH), 128.0 (2 x CH), 127.8 (CH), 127.6 (CH), 127.1 (C), 126.2 (CH), 125.1 (2 x CH), 124.5 (CH), 119.5 (CH), 76.4 (C), 43.8 (CH), 30.5 (CH₃), 16.9 (CH₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₀N₁O₁ [M+H]⁺: 278.1539, found: 278.1542. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 9.4 min, t_r (minor) = 16.6 min; 90% ee.

General Procedure C: Reductive Coupling of Vinylazaarenes Using Ligand L13 (0.30 mmol Scale)



A solution of the appropriate vinylazaarene (0.30 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3.0 mg, 0.015 mmol), ligand SL-T001-1 (**L13**) (10.3 mg, 0.015 mmol), and the appropriate ketone (0.33 mmol) in toluene (1.5 mL) was stirred at 0 °C for 15 min. PhSiH_3 (44 μL , 0.36 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give the reductive coupling product.



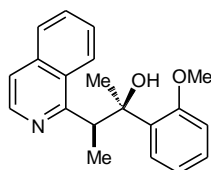
(2*R*,3*S*)-3-(Isoquinolin-1-yl)-2-[4-

(trifluoromethyl)phenyl]butan-2-ol (193e). The title compound

was prepared according to General Procedure C from 2-vinylisoquinoline **180c** (47 mg, 0.30 mmol) and 4-(trifluoromethyl)acetophenone (62 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (85 mg, 82%). m.p. 132-134 °C; $[\alpha]_{\text{D}}^{24}$ -106.7 (*c* 1.03, CHCl_3); IR (film) 3283 (OH), 2974, 1457, 1330, 1164, 1122, 1074, 1014, 850, 743 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.48 (1H, d, J = 5.7 Hz, ArH), 8.26 (1H, d, J = 8.4 Hz, ArH), 7.90 (1H, d, J = 8.1 Hz, ArH), 7.83 (2H, d, J = 8.1 Hz, ArH), 7.76 (1H, ddd, J = 8.1, 6.9, 1.1 Hz, ArH), 7.72-7.67 (3H, m, ArH), 7.66 (1H, br s, OH), 7.63 (1H, d, J = 5.7 Hz, ArH), 4.10 (1H, q, J = 7.0 Hz, CHCH_3), 1.38 (3H, s, CH_3COH), 1.11 (3H, d, J = 7.0 Hz, CHCH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 165.2 (C), 151.9 (C), 140.4 (CH), 136.6 (C), 130.5 (CH), 128.5 (C, q, J = 32.3 Hz), 127.9 (CH), 127.8 (CH), 127.0 (C), 125.6 (2 x CH), 125.0 (2 x CH, q, J = 3.7 Hz), 124.4 (C, q, J =

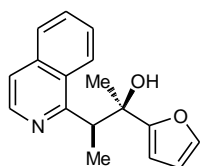
271.8 Hz), 124.4 (CH), 119.8 (CH), 76.4 (C), 43.6 (CH), 30.4 (CH₃), 16.8 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.2 (3F, s); HRMS (ESI) Exact mass calcd for C₂₀H₁₉F₃N₁O₁ [M+H]⁺: 346.1413, found: 346.1417. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 225 nm, 25 °C); t_r (major) = 7.4 min, t_r (minor) *ca.* 10 min (not detected); >99% ee.

Vapor diffusion of hexane into an EtOAc solution of **193e** gave crystals suitable for X-ray diffraction.



(2R,3S)-3-(Isoquinolin-1-yl)-2-(2-methoxyphenyl)butan-2-ol (193f).

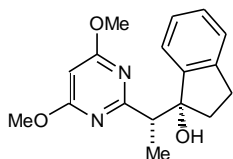
The title compound was prepared according to General Procedure c from 2-vinylisoquinoline **180c** (47 mg, 0.30 mmol) and 2'-methoxyacetophenone (46 μL, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (72 mg, 78%). m.p. 119-121 °C; [α]_D²⁴ -90.9 (*c* 1.06, CHCl₃); IR (film) 3290 (OH), 2970, 1487, 1388, 1363, 1236, 1063, 1027, 824, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.47 (1H, d, *J* = 5.7 Hz, ArH), 8.33 (1H, d, *J* = 8.3 Hz, ArH), 7.97 (1H, dd, *J* = 7.7, 1.8 Hz, ArH), 7.88 (1H, d, *J* = 7.7 Hz, ArH), 7.74 (1H, ddd, *J* = 8.1, 6.9, 1.2 Hz, ArH), 7.68 (1H, ddd, *J* = 8.2, 6.9, 1.4 Hz, ArH), 7.58 (1H, d, *J* = 5.7 Hz, ArH), 7.38 (1H, br s, OH), 7.30 (1H, ddd, *J* = 8.2, 7.5, 1.9 Hz, ArH), 7.07 (1H, td, *J* = 7.6, 1.1 Hz, ArH), 6.98 (1H, dd, *J* = 8.1, 0.9 Hz, ArH), 4.97 (1H, q, *J* = 7.1 Hz, CHCH₃), 4.00 (3H, s, OCH₃), 1.39 (3H, s, CH₃COH), 1.10 (3H, d, *J* = 7.1 Hz, CHCH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 166.3 (C), 155.6 (C), 140.5 (CH), 136.6 (C), 135.3 (C), 130.2 (CH), 128.2 (CH), 127.7 (2 x CH), 127.6 (C), 127.4 (CH), 124.9 (CH), 120.8 (CH), 119.3 (CH), 111.1 (CH), 76.2 (C), 55.5 (CH₃), 39.0 (CH), 27.9 (CH₃), 17.2 (CH₃); HRMS (ESI) Exact mass calcd for C₂₀H₂₂N₁O₂ [M+H]⁺: 308.1645, found: 308.1649. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 10.9 min, t_r (minor) = 30.0 min; 97% ee.



(2R,3S)-2-(Furan-2-yl)-3-(isoquinolin-1-yl)butan-2-ol (193g).

The title compound was prepared according to General Procedure C from 2-vinylisoquinoline **180c** (47 mg, 0.30 mmol) and 2-furyl methyl ketone

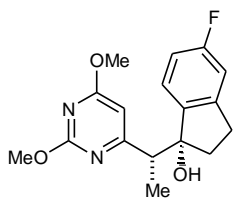
(36 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a yellow solid (61 mg, 76%). m.p. 60-62 °C; $[\alpha]_D^{24}$ -103.9 (*c* 1.02, CHCl₃); IR (film) 3278 (OH), 2977, 1560, 1457, 1357, 1073, 1001, 937, 824, 731 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.44 (1H, d, *J* = 5.7 Hz, ArH), 8.28 (1H, d, *J* = 8.5 Hz, ArH), 7.87 (1H, d, *J* = 8.1 Hz, ArH), 7.74 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz, ArH), 7.66 (1H, ddd, *J* = 8.3, 6.9, 1.3 Hz, ArH), 7.59 (1H, d, *J* = 5.7 Hz, ArH), 7.43 (1H, dd, *J* = 1.8, 0.9 Hz, ArH), 7.41 (1H, br s, OH), 6.46 (1H, dd, *J* = 3.2, 0.9 Hz, ArH), 6.41 (1H, dd, *J* = 3.2, 1.8 Hz, ArH), 4.19 (1H, q, *J* = 7.0 Hz, CHCH₃), 1.37 (3H, s, CH₃COH), 1.22 (3H, d, *J* = 7.1 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 165.6 (C), 159.5 (C), 140.7 (CH), 140.4 (CH), 136.5 (C), 130.4 (CH), 127.7 (CH), 127.6 (CH), 127.1 (C), 124.7 (CH), 119.6 (CH), 110.3 (CH), 105.0 (CH), 75.2 (C), 41.7 (CH), 28.4 (CH₃), 17.2 (CH₃); HRMS (ESI) Exact mass calcd for C₁₇H₁₈N₁O₂ [M+H]⁺: 268.1332, found: 268.1335. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 225 nm, 25 °C); *t*_r (major) = 11.7 min, *t*_r (minor) = 18.6 min; 89% ee.



(R)-1-[(R)-1-(4,6-Dimethoxypyrimidin-2-yl)ethyl]indan-1-ol (193i). The title compound was prepared according to a slight modification of General Procedure C from 2-vinylpyrimidine **180e**

(50 mg, 0.30 mmol) and 1-indanone (44 mg, 0.33 mmol) in that the reaction was stirred for 4 h at room temperature (rather than 15 h), and purified by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) to give a colorless gum (76 mg, 85%). $[\alpha]_D^{24}$ -32.1 (*c* 1.00, CHCl₃); IR (film) 3419 (OH), 1591, 1463, 1372, 1251, 1190, 1164, 1044, 830, 763 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.25-7.17 (2H, m, ArH), 7.14-7.07 (1H, m, ArH), 6.88 (1H, d, *J* = 7.6 Hz, ArH), 6.14 (1H, br s, OH), 5.99 (1H, s, ArH), 3.94 (6H, s, 2 x OCH₃), 3.32 (1H, q, *J* = 7.1 Hz, CHCH₃), 3.10-3.00 (1H, m, ArCH₂), 2.89-2.79 (1H, m, ArCH₂), 2.39 (1H, ddd, *J* = 13.2, 8.4, 4.8 Hz, ArCH₂CH₂), 2.09 (1H, ddd, *J* = 13.4, 8.8, 6.5 Hz, ArCH₂CH₂), 1.33 (3H, d, *J* = 7.1 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.0 (C), 170.8 (2 x C), 146.9 (C), 143.3 (C), 127.8 (CH), 126.4 (CH), 124.8 (CH), 123.0 (CH), 87.8 (CH), 85.4 (C), 54.1 (2 x CH₃), 48.9 (CH), 36.9 (CH₂), 29.7 (CH₂), 15.2 (CH₃); HRMS (ESI) Exact mass calcd for C₁₇H₂₀N₂O₃Na₁ [M+Na]⁺:

323.1366, found: 323.1370. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 12.5 min, t_r (major) = 15.4 min; 96% ee.

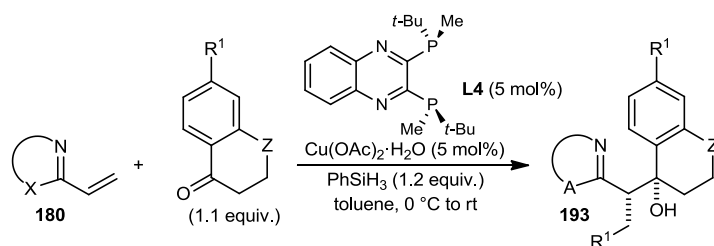


(R)-1-[(R)-1-(2,6-Dimethoxypyrimidin-4-yl)ethyl]5-fluoro-indan-1-ol (193j). The title compound was prepared according to a slight

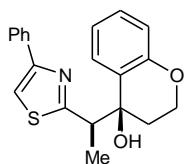
modification of General Procedure C from 2-vinylpyrimidine **180f** (50 mg, 0.30 mmol) and 5-fluoro-1-indanone (50 mg, 0.33 mmol) in

that the reaction was stirred for 3 h at room temperature (rather than 15 h), and purified by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) to give a colorless gum (60 mg, 63%). $[\alpha]_D^{24} -71.7$ (c 0.78, CHCl_3); IR (film) 3375 (OH), 2949, 1597, 1462, 1361, 1247, 1205, 1111, 1029, 842 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.87 (1H, dd, J = 8.9, 1.2 Hz, ArH), 6.83-6.73 (2H, m, ArH), 6.16 (1H, s, ArH), 6.05 (1H, br s, OH), 4.03 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 3.08-2.93 (2H, m, CHCH_3 and ArCH_2), 2.85-2.73 (1H, m, ArCH_2), 2.42-2.33 (1H, m, ArCH_2CH_2), 2.08 (1H, ddd, J = 13.5, 8.9, 7.3 Hz, ArCH_2CH_2), 1.28 (3H, d, J = 7.1 Hz, CHCH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 173.7 (C), 172.2 (C), 164.5 (C), 162.9 (C, d, J = 244.8 Hz), 145.2 (C, d, J = 8.3 Hz), 142.6 (C, d, J = 2.4 Hz), 124.5 (CH, d, J = 9.1 Hz), 113.6 (CH, d, J = 22.7 Hz), 111.5 (CH, d, J = 21.8 Hz), 100.7 (CH), 84.9 (C), 54.9 (CH_3), 53.9 (CH_3), 46.9 (CH), 37.5 (CH_2), 29.4 (CH_2 , d, J = 2.0 Hz), 15.5 (CH_3); ^{19}F NMR (376 MHz, CDCl_3) δ -115.3 (1F, s); HRMS (ESI) Exact mass calcd for $\text{C}_{17}\text{H}_{20}\text{F}_1\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 319.1452, found: 319.1454. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 25.4 min, t_r (major) = 39.2 min; 93% ee.

General Procedure D: Reductive Coupling of Vinylazaarenes Using Ligand L11 (0.30 mmol Scale)



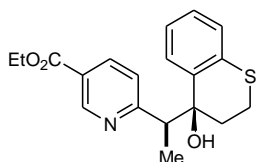
A solution of the appropriate vinylazaarene (0.30 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (3.0 mg, 0.015 mmol), (R,R) -Quinox-P* (**L11**) (5.0 mg, 0.015 mmol), and the appropriate ketone (0.33 mmol) in toluene (1.5 mL) was stirred at 0 °C for 15 min. PhSiH_3 (44 μL , 0.36 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give the reductive coupling product.



(R)-4-[(S)-1-(4-Phenylthiazol-2-yl)ethyl]chroman-4-ol (193k). The title compound was prepared according to General Procedure D from 2-vinylthiazole **180g** (56 mg, 0.30 mmol) and 4-chromanone (49 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (69 mg, 68%). m.p. 100-102 °C; $[\alpha]_{\text{D}}^{24} +128.7$ (*c* 0.87, CHCl_3); IR (film) 3378 (OH), 1607, 1487, 1450, 1255, 1221, 1124, 1058, 805, 757 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.95-7.89 (2H, m, ArH), 7.51-7.43 (4H, m, ArH), 7.41-7.35 (1H, m, ArH), 7.21 (1H, ddd, $J = 8.3, 7.2, 1.6$ Hz, ArH), 6.99 (1H, td, $J = 7.8, 1.3$ Hz, ArH), 6.89 (1H, dd, $J = 8.2, 1.2$ Hz, ArH), 6.05 (1H, br s, OH), 4.27-4.17 (2H, m, OCH_2), 3.99 (1H, q, $J = 7.2$ Hz, CHCH_3), 2.18-2.09 (1H, m, OCH_2CH_2), 1.62-1.54 (1H, m, OCH_2CH_2), 1.25 (3H, d, $J = 7.2$ Hz, CHCH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 174.5 (C), 155.7 (C), 155.3 (C), 133.8 (C), 129.0 (CH), 128.9 (2 x CH), 128.5 (CH), 127.2 (CH), 126.3 (2 x CH), 125.6 (C), 121.1 (CH), 117.4 (CH), 111.9 (CH), 71.2 (C), 62.8 (CH_2), 45.9 (CH), 31.9 (CH_2), 15.7 (CH_3); HRMS (ESI) Exact mass calcd for $\text{C}_{20}\text{H}_{20}\text{N}_1\text{O}_2\text{S}_1$ $[\text{M}+\text{H}]^+$: 338.1209, found: 338.1209. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column

(98:2 hexane:*i*-PrOH, 0.8 mL/min, 250 nm, 25 °C); t_r (minor) = 28.3 min, t_r (major) = 47.3 min; 93% ee.

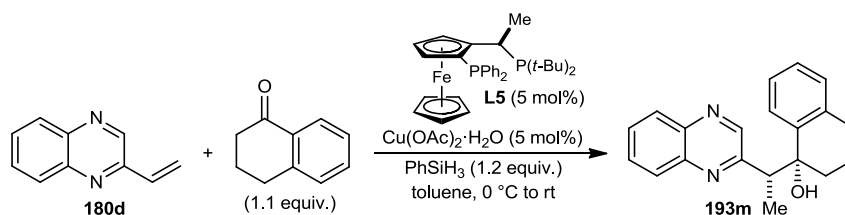
Vapor diffusion of hexane into an EtOAc solution of **193k** gave crystals suitable for X-ray diffraction.



Ethyl 6-[(*S*)-1-[(*S*)-4-Hydroxythiochroman-4-yl]ethyl]pyridine-3-carboxylate (193l**)**. The title compound was prepared according

to General Procedure D from 2-vinylpyridine **180j** (53 mg, 0.30 mmol) and thiocroman-4-one (54 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) to give a white solid (68 mg, 66%). m.p. 108-110 °C; $[\alpha]_D^{24}$ -217.8 (*c* 1.01, CHCl₃); IR (film) 3433 (OH), 1718, 1646, 1467, 1438, 1391, 1368, 1289, 1117, 1027 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.16 (1H, dd, *J* = 2.1, 0.5 Hz, ArH), 8.02 (1H, dd, *J* = 8.1, 2.2 Hz, ArH), 7.06 (1H, dd, *J* = 7.8, 1.1 Hz, ArH), 6.94 (1H, td, *J* = 7.6, 1.5 Hz, ArH), 6.86-6.79 (2H, m, ArH), 6.74 (1H, br s, OH), 6.73-6.67 (1H, m, ArH), 4.40 (2H, q, *J* = 7.1 Hz, OCH₂), 3.59 (1H, q, *J* = 7.0 Hz, CHCH₃), 3.20-3.13 (2H, m, SCH₂), 2.52 (1H, dt, *J* = 13.7, 4.5 Hz, SCH₂CH₂), 2.03-1.92 (1H, m, SCH₂CH₂), 1.46-1.38 (6H, m, CHCH₃ and OCH₂CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 168.0 (C), 165.0 (C), 149.3 (CH), 140.8 (C), 137.9 (CH), 131.6 (C), 126.8 (CH), 126.1 (CH), 125.5 (CH), 124.5 (C), 123.6 (CH), 123.3 (CH), 73.9 (C), 61.4 (CH₂), 43.3 (CH), 31.9 (CH₂), 22.5 (CH₂), 14.8 (CH₃), 14.2 (CH₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₂NO₃S [M+H]⁺: 344.1315, found: 344.1318. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 33.3 min, t_r (major) = 38.5 min; 91% ee.

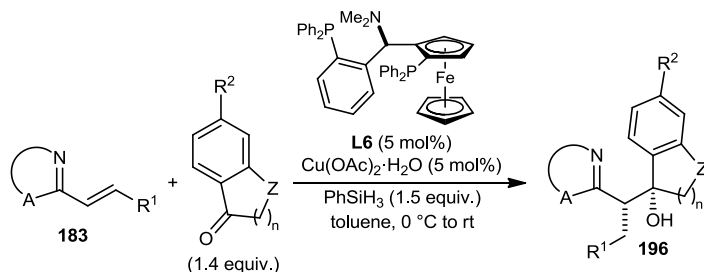
(*R*)-1-[(*R*)-1-Quinoxalin-2-ylethyl]-1,2,3,4-tetrahydronaphthalen-1-ol (193m**)**



A solution of 2-vinylquinoxaline **180d** (47 mg, 0.30 mmol), Cu(OAc)₂·H₂O (3.0 mg, 0.015 mmol), SL-J002-1 (**L12**) (8.1 mg, 0.015 mmol), and α -tetralone (44 μ L, 0.33

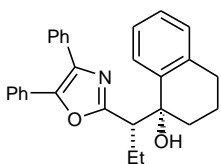
mmol) in toluene (1.5 mL) was stirred at 0 °C for 15 min. PhSiH₃ (44 μL, 0.36 mmol) was then added dropwise. The mixture was stirred at 0 °C for 30 min, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (10% EtOAc/hexane→25% EtOAc/hexane) to give the *tertiary alcohol* **193m** (65 mg, 71%) as a yellow gum. $[\alpha]_{\text{D}}^{24} +161.0$ (*c* 1.18, CHCl₃); IR (film) 3434 (OH), 2936, 1645, 1490, 1450, 1372, 1219, 1129, 1024, 764 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.59 (1H, s, ArH), 8.13 (1H, dd, *J* = 8.3, 1.3 Hz, ArH), 8.10 (1H, dd, *J* = 8.2, 1.4 Hz, ArH), 7.81 (1H, ddd, *J* = 8.4, 7.0, 1.6 Hz, ArH), 7.76 (1H, ddd, *J* = 8.3, 7.0, 1.6 Hz, ArH), 7.14-7.08 (2H, m, ArH), 7.02 (1H, d, *J* = 7.8 Hz, ArH), 6.98-6.92 (1H, m, ArH), 4.87 (1H, br s, OH), 3.77 (1H, q, *J* = 7.2 Hz, CHCH₃), 2.86 (2H, t, *J* = 6.7 Hz, ArCH₂), 2.26-2.18 (1H, m, ArCH₂CH₂CH₂), 1.98-1.84 (2H, m, ArCH₂CH₂CH₂), 1.68-1.59 (1H, m, ArCH₂CH₂CH₂), 1.39 (3H, d, *J* = 7.2 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 158.8 (C), 146.5 (CH), 141.6 (C), 141.5 (C), 141.0 (C), 136.9 (C), 130.1 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 127.0 (CH), 126.0 (CH), 125.8 (CH), 75.1 (C), 47.0 (CH), 33.0 (CH₂), 29.2 (CH₂), 18.8 (CH₂), 14.9 (CH₃); HRMS (ESI) Exact mass calcd for C₂₀H₂₁N₂O₁ [M+H]⁺: 305.1648, found: 305.1652. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); *t*_r (major) = 33.8 min, *t*_r (minor) = 42.1 min; 96% ee.

General Procedure E: Reductive Coupling of Alkenylazaarenes Using Ligand L13 (0.30 mmol Scale)



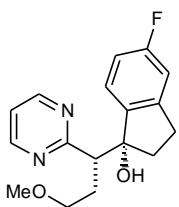
A solution of the appropriate alkenylazaarene (0.30 mmol), Cu(OAc)₂·H₂O (3.0 mg, 0.015 mmol), ligand SL-T001-1 (**L13**) (10.3 mg, 0.015 mmol), and the appropriate

ketone (0.42 mmol) in toluene (1.5 mL) was stirred at 0 °C for 15 min. PhSiH₃ (56 µL, 0.45 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 3–4 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give the reductive coupling product.



(R)-1-[(S)-1-(4,5-Diphenyloxazol-2-yl)-propyl]-1,2,3,4-tetrahydronaphthalen-1-ol (196a). The title compound was prepared

according to General Procedure E from alkenylazaarene **183a** (78 mg, 0.30 mmol) and α -tetralone (56 µL, 0.42 mmol) for a reaction time of 3 h at room temperature, and purified by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) to give a colorless gum (77 mg, 63%). $[\alpha]_D^{24}$ –21.6 (*c* 1.11, CHCl₃); IR (film) 3418 (OH), 2932, 1604, 1556, 1443, 1219, 1060, 920, 764, 693 cm^{–1}; ¹H NMR (500 MHz, CDCl₃) δ 7.78–7.71 (2H, m, ArH), 7.64–7.57 (2H, m, ArH), 7.51–7.45 (1H, m, ArH), 7.45–7.32 (6H, m, ArCH), 7.25–7.18 (2H, m, ArH), 7.17–7.09 (1H, m, ArH), 3.93 (1H, br s, OH), 3.59 (1H, dd, *J* = 11.6, 2.7 Hz, CHCH₂), 2.90–2.72 (2H, m, ArCH₂), 2.20–2.09 (1H, m, CH₂), 2.08–1.79 (4H, m, CH₂), 1.48–1.35 (1H, m, CH₂), 0.94 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 163.8 (C), 145.4 (C), 139.9 (C), 137.9 (C), 135.0 (C), 132.2 (C), 129.1 (CH), 128.9 (C), 128.6 (2 x CH), 128.5 (2 x CH), 128.5 (CH), 128.1 (CH), 127.9 (2 x CH), 127.2 (CH), 126.6 (2 x CH), 126.4 (CH), 125.8 (CH), 74.0 (C), 52.2 (CH), 33.4 (CH₂), 30.0 (CH₂), 21.9 (CH₂), 19.0 (CH₂), 13.0 (CH₃); HRMS (ESI) Exact mass calcd for C₂₈H₂₈N₁O₂ [M+H]⁺: 410.2115, found: 410.2114. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); *t*_r (major) = 22.2 min, *t*_r (minor) = 32.6 min; 93% ee.

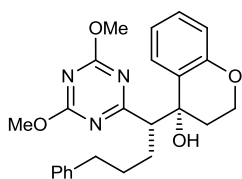


(R)-5-Fluoro-1-[(R)-3-methoxy-1-pyrimidin-2-yl-propyl]indan-1-ol (196b). The title compound was prepared according to General Procedure

E from alkenylazaarene **183b** (45 mg, 0.30 mmol) and 5-fluoro-1-

indanone (52 μ L, 0.42 mmol) for a reaction time of 3 h at room temperature, and purified by column chromatography (20% EtOAc/hexane \rightarrow 90% EtOAc/hexane) to give a white solid **5c** (67 mg, 74%). m.p 80-82 $^{\circ}$ C; $[\alpha]_{\text{D}}^{24}$ +61.9 (*c* 1.07, CHCl₃); IR (film) 3395 (OH), 2931, 1562, 1485, 1421, 1245, 1120, 772, 637, 456 cm^{-1} ; ^1H NMR (500 MHz, CDCl₃) δ 8.71 (2H, d, *J* = 3.7 Hz, ArH), 7.31-7.20 (1H, m, ArH), 6.85 (1H, dd, *J* = 8.9, 2.2 Hz, ArH), 6.63 (1H, td, *J* = 8.9, 2.3 Hz, ArH), 6.38 (1H, dd, *J* = 5.3, 8.3 Hz, ArH), 5.41 (1H, br s, OH), 3.37 (1H, dd, *J* = 11.1, 1.9 Hz, CHCH₂), 3.30-3.23 (1H, m, OCH₂), 3.23-3.13 (4H, m, OCH₃ and OCH₂), 2.99-2.90 (1H, m, ArCH₂), 2.89-2.79 (1H, m, ArCH₂), 2.65-2.50 (1H, m, ArCH₂CH₂), 2.40-2.28 (1H, m, ArCH₂CH₂), 2.17-2.06 (2H, m, OCH₂CH₂); ^{13}C NMR (125.8 MHz, CDCl₃) δ 171.5 (C), 162.7 (C, d, *J* = 244.8 Hz), 156.6 (2 x CH), 145.2 (C, d, *J* = 8.3 Hz), 142.8 (C), 123.7 (CH, d, *J* = 9.1 Hz), 119.4 (CH), 113.3 (CH, d, *J* = 22.7 Hz), 111.7 (CH, d, *J* = 21.8 Hz), 84.7 (C), 70.7 (CH₂), 58.4 (CH₃), 52.0 (CH), 37.7 (CH₂), 30.5 (CH₂), 29.2 (CH₂, d, *J* = 2.0 Hz); ^{19}F NMR (376 MHz, CDCl₃) δ -115.3 (1F, s); HRMS (EIS) Exact mass calcd for C₁₇H₂₀F₁N₂O₂ [M+H]⁺: 303.1503, found: 303.1498. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 $^{\circ}$ C); *t_r* (minor) = *ca.* 18 min (not detected), *t_r* (major) = 23.3 min; >99% ee.

Vapor diffusion of hexane into an EtOAc solution of **196b** gave crystals suitable for X-ray diffraction.

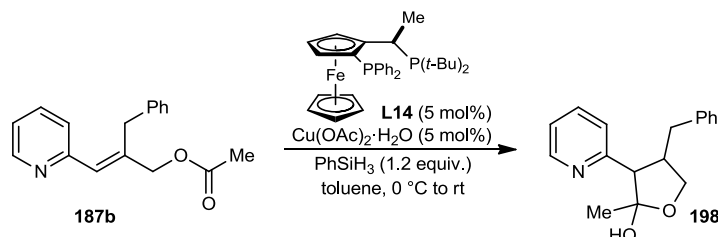


(R)-4-[(R)-1-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-4-phenylbutyl]chroman-4-ol (196c). The title compound was prepared according to General Procedure E from alkenylazaarene **183c** (77 mg, 0.30 mmol) and 4-chromanone (62 mg, 0.42 mmol) for a reaction time of

4 h at room temperature, and purified by column chromatography (10% EtOAc/hexane \rightarrow 40% EtOAc/hexane) to give a yellow gum (95 mg, 75%). $[\alpha]_{\text{D}}^{24}$ +8.6 (*c* 0.93, CHCl₃); IR (film) 3383 (OH), 2966, 1559, 1502, 1452, 1360, 1222, 1110, 754, 446 cm^{-1} ; ^1H NMR (500 MHz, CDCl₃) δ 7.33 (1H, dd, *J* = 7.9, 1.4 Hz, ArH), 7.25-7.10 (4H, m, ArH), 7.05 (2H, d, *J* = 7.0 Hz, ArH), 6.93-6.88 (1H, m, ArH), 6.86 (1H, dd, *J* = 8.2, 1.1 Hz, ArH), 4.39 (1H, br s, OH), 4.26-4.15 (2H, m, OCH₂), 4.02 (6H, s, 2 x OCH₃), 3.53 (1H, dd, *J* = 11.3, 2.1 Hz, CHCH₂), 2.55 (1H, ddd, *J* = 14.8, 9.1, 6.2 Hz, PhCH₂),

2.50-2.40 (1H, m, PhCH₂), 2.32 (1H, ddd, *J* = 14.5, 10.2, 4.4 Hz, OCH₂CH₂), 2.18-2.05 (1H, m, OCH₂CH₂), 1.83 (1H, ddd, *J* = 14.3, 4.9, 2.9 Hz, PhCH₂CH₂CH₂), 1.59-1.40 (2H, m, PhCH₂CH₂CH₂), 1.35-1.24 (1H, m, PhCH₂CH₂CH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 182.7 (C), 171.8 (C), 155.1 (C), 141.8 (C), 129.0 (CH), 128.1 (4 x CH), 126.5 (C), 125.8 (CH), 125.6 (CH), 120.8 (CH), 117.4 (CH), 70.7 (C), 62.6 (CH₂), 55.9 (CH), 55.2 (2 x CH₃), 35.4 (CH₂), 32.0 (CH₂), 29.8 (CH₂), 28.0 (CH₂); HRMS (ESI) Exact mass calcd for C₂₄H₂₇N₃O₄Na₁ [M+Na]⁺: 444.1894, found: 444.1895. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); *t*_r (minor) = 27.4 min, *t*_r (major) = 30.8 min; 96% ee.

4-Benzyl-2-methyl-3-(pyridine-2-yl)tetrahydrofuran-2-ol (**198**)



A solution of 2-alkenylpyridine **187b** (107 mg, 0.40 mmol), Cu(OAc)₂·H₂O (4.0 mg, 0.02 mmol) and ligand SL-J001-1 (**L14**) (12.8 mg, 0.02 mmol) in toluene (2 mL) was stirred at 0 °C for 15 min. PhSiH₃ (59 μL, 0.48 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (10% EtOAc/hexane→25% EtOAc/hexane) to give the hemiketal **198** (65 mg, 71%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 8.56-8.54 (1H, m, ArH), 7.60 (1H, td, *J* = 7.7, 1.7 Hz, ArH), 7.22-7.17 (3H, m, ArH), 7.16-7.12 (1H, m, ArH), 7.08-7.02 (3H, m, ArH), 4.25 (1H, t, *J* = 8.5 Hz, CHCH₂O), 3.76 (1H, dd, *J* = 8.5, 7.2 Hz, CHCH₂O), 3.21-3.15 (1H, m, PhCH₂CH), 2.94 (1H, d, *J* = 10.2 Hz, N=CCH), 2.78 (1H, dd, *J* = 13.8, 6.0 Hz, PhCH₂), 2.73 (1H, dd, *J* = 14.0, 9.2 Hz, PhCH₂), 1.45 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 161.2 (C), 151.3 (CH), 142.2 (C), 139.7 (CH), 131.23 (CH), 131.0 (CH), 128.9 (CH), 127.9 (CH), 124.8 (CH),

107.7 (C), 73.9 (CH₂), 62.5 (CH), 49.6 (CH), 42.0 (CH₂), 28.8 (CH₃); m/z (ES) 292 ([M+Na]⁺, 100).

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Aromatic Heterocycles as Activating Groups for Asymmetric Conjugate Addition Reactions. Enantioselective Copper-Catalyzed Reduction of 2-Alkenylheteroarenes

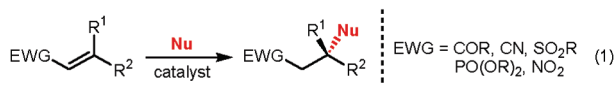
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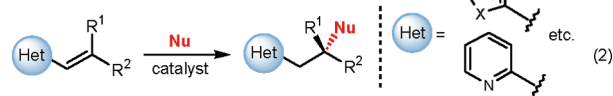
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The 1,4-addition of a nucleophile to an alkene conjugated to an electron-withdrawing group is a fundamental reaction in organic chemistry, and numerous catalytic asymmetric variants (eq 1) of this process are now routinely employed in the synthesis of molecules of interest.^{1,2} The most common functional groups used to activate alkenes toward asymmetric conjugate additions include carbonyls, nitriles, sulfones, phosphonates, and nitro groups. We recently questioned whether other rarely considered yet common functional groups might also be employed in this capacity, and our attention focused on nitrogen-containing aromatic heterocycles. Given that heteroarenes such as oxazoles, thiazoles, pyridines, and others are ubiquitous in biologically active natural products, pharmaceuticals, and agrochemicals, the ability to functionalize these privileged structures through a diverse set of asymmetric conjugate additions of 2-alkenyl derivatives (eq 2) would open up broad-ranging applications.

Catalytic asymmetric conjugate additions:



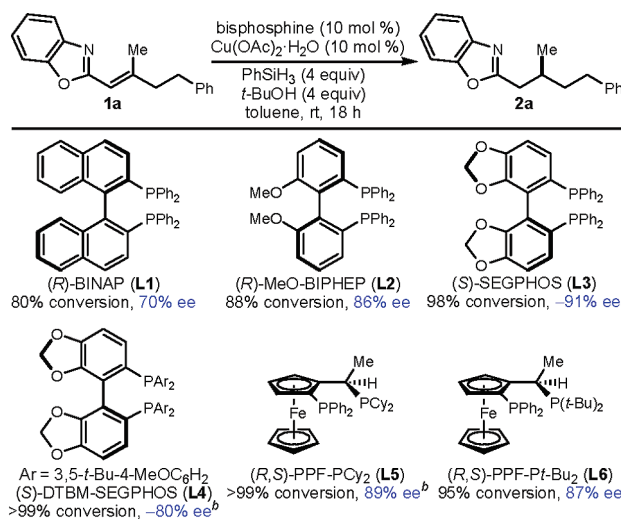
Aromatic heterocycles as substrates?



Although conjugate additions to 2-vinylheteroarenes (R¹, R² = H in eq 2) are relatively common,³ the corresponding reactions of substrates containing a β -substituent are much rarer, presumably for steric reasons.^{4,5} Furthermore, the only report of a catalytic enantioselective variant is limited to poorly selective ($\leq 15\%$ ee) Grignard additions to 4-alkenylpyridines.⁵ Therefore, we recently initiated a program targeted at addressing these deficiencies, and in this communication, our preliminary findings involving highly enantioselective copper-catalyzed reductions⁶ of β,β' -disubstituted 2-alkenylheteroarenes are presented.

The asymmetric copper-catalyzed conjugate reduction of activated alkenes is a well-established method for the synthesis of various useful chiral building blocks.^{6–10} Whether a nitrogen-containing heteroarene would provide sufficient activation to an adjacent alkene in an analogous reaction was, however, uncertain. In addition, it seemed likely that coordination of the Lewis basic nitrogen of the heteroarene to the copper catalyst would occur in such a process, and whether this interaction would be beneficial, inconsequential, or detrimental was not easy to predict.

Our investigations began with a survey of chiral bisphosphines **L1**–**L6** using 2-alkenylbenzoxazole **1a** as a test substrate (Table 1). Using 10 mol % of Cu(OAc)₂·H₂O, 10 mol % of ligand, and 4 equiv each of PhSiH₃ and *t*-BuOH in toluene at room temperature, biaryl-based ligands **L1**–**L4** proved competent in promoting conjugate reduction.¹¹ With (*R*)-BINAP (**L1**), both conversion and enantioselectivity were only moderate. However, improved results were observed using (*R*)-MeO-BIPHEP (**L2**) and the

Table 1. Ligand Optimization for the Asymmetric Reduction of **1a**^a

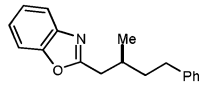
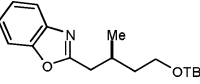
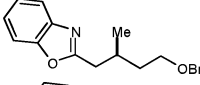
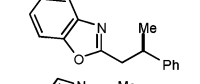
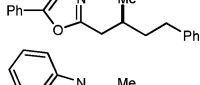
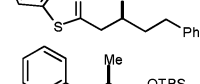
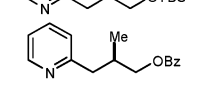
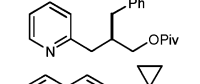
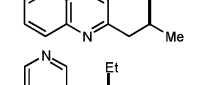
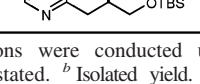
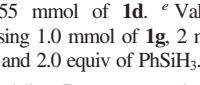
^a Reactions were conducted using 0.20 mmol of **1a** in toluene (1 mL). Conversions were determined by GC analysis. Enantioselectivities were determined by chiral HPLC analysis. ^b Reactions complete after 2 h.

SEGPHOS ligands **L3** and **L4**, with 91% ee obtained using (*S*)-SEGPHOS (**L3**). The Josiphos ligands **L5** and **L6** were also effective, providing **2a** in 89% and 87% ee, respectively. Of all the ligands, the highest reaction rates were observed with **L4** and **L5** (reactions were complete in 2 h). However, the superior selectivity provided by **L5** prompted us to select this ligand for further optimization and investigation of the reaction scope.

Using 5 mol % each of Cu(OAc)₂·H₂O and **L5**, PhSiH₃ (1.5 equiv), and *t*-BuOH (2.0 equiv) at an initial temperature of 0 °C, a range of β,β' -disubstituted 2-alkenylheteroarenes underwent conjugate reduction with generally excellent levels of enantioselection (Table 2).¹¹ In addition to benzoxazole (entries 1–4), other effective nitrogen-containing heteroarenes in this process included 5-phenyloxazole (entry 5), benzothiazole (entry 6), pyridine (entries 7–9), quinoline (entry 10), and pyrazine (entry 11). Tolerated functionality at the β -positions of the alkene included simple aliphatic groups, a phenyl group (entry 4), a benzyl group (entry 9), various oxygenated alkyl groups (entries 2, 3, 7–9, and 11), and a cyclopropane (entry 10). The process is tolerant of lower loadings of copper and ligand. For example, reduction of **1g** on a 1.0 mmol scale using 2 mol % each of Cu(OAc)₂·H₂O and **L5** provided **2g** in 92% yield and 96% ee (entry 7, values in parentheses).

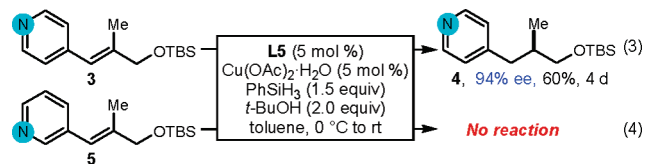
Experiments to explore the origins of reactivity were then conducted. Reduction of 4-alkenylpyridine **3** provided **4** in 60% yield and 94% ee, albeit in a slower reaction that was incomplete even after 4 days (eq 3). This result suggests that alkene reduction by copper hydride can occur without assistance of a directing effect from the nitrogen atom. In contrast,

Table 2. Scope of Cu-Catalyzed Asymmetric Conjugate Reduction^a

entry	product	yield (%) ^b	ee (%) ^c
1		2a 90	93
2		2b 67	94
3		2c 88	95
4 ^d		2d 95	87
5		2e 93	90
6		2f 86	95
7		2g 90 (92) ^e	>99 (96) ^e
8 ^f		2h 81	98
9		2i 90	97
10		2j 90	96
11		2k 89	96

^a Reactions were conducted using 0.20 mmol of **1a–1k** unless otherwise stated. ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d Using 0.155 mmol of **1d**. ^e Values in parentheses refer to a reaction conducted using 1.0 mmol of **1g**, 2 mol % Cu, and 2 mol % **L5**. ^f Using 0.10 mmol of **1h** and 2.0 equiv of PhSiH₃.

3-alkenylpyridine **5** was unreactive (eq 4), demonstrating the importance of conjugation of the alkene to a C=N moiety for reactivity.



In summary, copper-catalyzed asymmetric conjugate reductions of β,β' -disubstituted 2-alkenylheteroarenes are reported. In addition to serving as a further demonstration of the power of chiral copper hydride catalysis,⁶ this work has shown nitrogen-containing aromatic heterocycles can provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate addition reactions. Extension of the general concept to other classes of asymmetric reactions should provide a range of useful tools for chemists working with heteroarenes. Future studies from our laboratory will be directed toward this goal.

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Supporting Information Available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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EDGE ARTICLE

Enantioselective rhodium-catalyzed arylation of electron-deficient alkenylarenes†‡

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β -Substituted alkenyl-*para*-nitroarenes, an unexplored substrate class for catalytic asymmetric addition reactions, undergo highly enantioselective rhodium-catalyzed arylations with arylboronic acids in the presence of a dibenzylamide-containing chiral diene ligand. One example of the asymmetric arylation of an alkenyl-*p*-cyano-*m*-(trifluoromethyl)benzene is also presented.

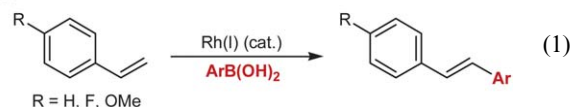
Catalytic enantioselective additions of organometallic reagents to activated alkenes are an important class of reactions for the production of enantioenriched chiral compounds.¹ However, examples of such processes where alkenes are activated by arenes or heteroarenes are uncommon, presumably due to the relatively low levels of activation that (hetero)arenes provide. Given the ubiquitous nature of (hetero)arenes in compounds for applications ranging from biology to materials science, the development of reactions that address this deficiency is highly desirable.

Our group has demonstrated that heteroarenes containing a suitably placed C=N moiety are able to activate alkenes² towards enantioselective copper-catalyzed reductions³ and rhodium-catalyzed arylations,⁴ while Bernadi, Adamo, and co-workers have developed asymmetric additions of nitroalkanes to 4-nitro-5-styrylisoxazoles.⁵ For alkenes conjugated to simple arenes (which in general provide only minimal activation), highly reactive organometallic reagents are usually required.⁶ A number of groups have reported stoichiometric or catalytic enantioselective carbolithiations^{7,8} of various alkenylarenes^{9–11} mediated by (–)-sparteine^{9,10} or a (+)-sparteine surrogate.¹¹ Although these carbolithiations work well, the development of processes that proceed under milder conditions, employing organometallic reagents that exhibit greater functional group compatibility, represents an unmet need. In this paper, the catalytic enantioselective addition of arylboronic acids to alkenes conjugated to electron-deficient arenes is described.

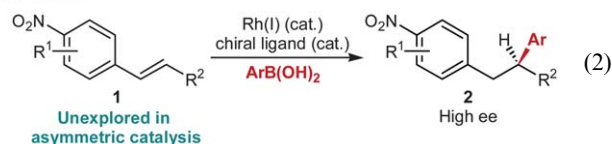
The rhodium-catalyzed asymmetric 1,4-addition of arylboron compounds to β -substituted electron-deficient alkenes is now a well-established method for the preparation of chiral

compounds.^{12–14} Since the initial discovery of enones as substrates for these reactions,¹² subsequent efforts have extended the scope of the acceptor¹⁵ to alkenes conjugated to a range of common electron-withdrawing groups.^{16–22} More recently, less common activating groups have been employed. In addition to our report on asymmetric arylations of alkenylheteroarenes,⁴ which builds upon work by Lautens and co-workers describing non-enantioselective additions of boronic acids to vinylazines,²³ Sasaki and Hayashi have disclosed the asymmetric arylation of borylalkenes.²⁴ However, rhodium-catalyzed addition of arylboron compounds to alkenylarenes has not, to our knowledge, been described. Instead, simple styrenes (where activation of the alkene is minimal) were shown by the Lautens group to undergo Heck-type reactions under aqueous conditions using water-soluble phosphine ligands (eqn (1)).²³

Ref. 23:



This work:



It occurred to us that placement of the strongly electron-withdrawing nitro group at the *para*-position of the arene might lead to sufficient polarization of the alkene to the point where addition products **2**, rather than Heck-type products, would form, even for 1,2-disubstituted alkenes (eqn (2)). Although nitroalkenes have been successfully employed in myriad additions of carbon nucleophiles,^{19,25} the analogous reactions of their phenylogous counterparts **1** are extremely rare,^{6c–h} and no

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† Dedicated to the memory of Hamish McNab.

‡ Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for new compounds, and crystallographic data. CCDC reference number 809081. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1sc00521a

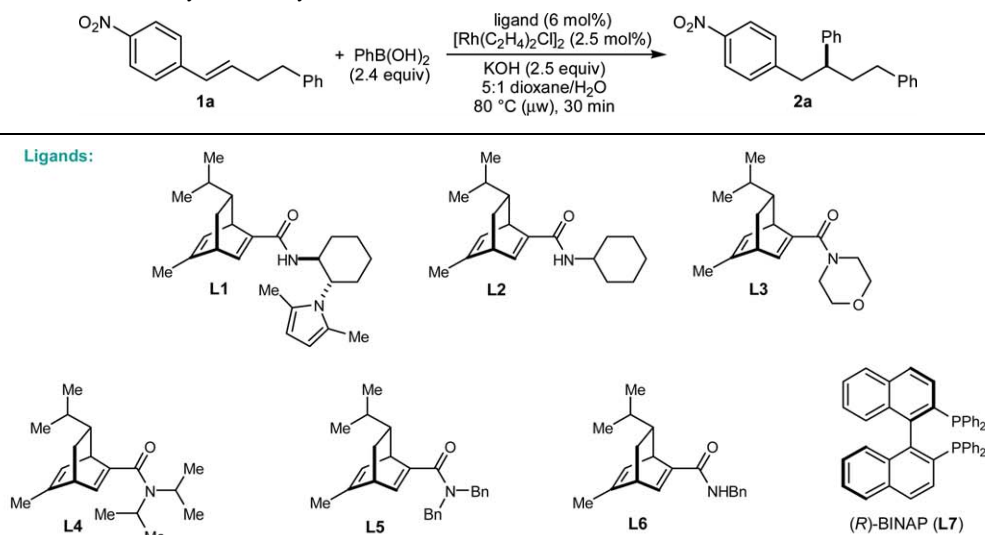
asymmetric reactions have been reported. Therefore, the successful realization of the reactions depicted in eqn (2) was an attractive goal and would set the stage for the use of this under-exploited class of electrophiles in other catalytic enantioselective addition reactions.

Our initial experiments focused upon alkenyl-*p*-nitroarene **1a** as a test substrate (Table 1). As a preliminary gauge of reactivity, the addition of PhB(OH)_2 to **1a** was performed using $[\text{Rh}(\text{cod})\text{Cl}]_2$ (2.5 mol%) and KOH (2.5 equiv.) in dioxane/ H_2O at 80 °C under microwave (μw) irradiation²⁶ for 30 min. This experiment resulted in 42% conversion into *rac*-**2a** (entry 1). Next, the use of chiral ligands was evaluated in combination with $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ as a precatalyst to assess whether **2a** could be obtained with improved conversions and in high enantioselectivity. Chiral diene ligands have been shown to provide excellent results in asymmetric 1,4-arylation reactions^{27–29} and, in view of the success obtained with secondary amide-containing ligand **L1**³⁰ in our study of the asymmetric arylation of alkenylheteroarenes,⁴ this diene was evaluated first. Although **L1** did lead to **2a** in 97% ee, the conversion was only 35% (entry 2). Increasing the temperature to 120 °C did increase the conversion with only a slight impact upon enantioselection (95% ee), but appreciable starting material remained (entry 3). Additional amide-containing chiral

dienes were then investigated. The enantioselectivity remained high with ligand **L2** that lacks the pyrrole on the cyclohexyl ring, but the conversion was low (entry 4). Ligand **L3**⁴ containing a morpholine amide provided improved conversion (76%) at 80 °C, but the product was formed in only 70% ee (entry 5). Ligands **L4** and **L5** containing tertiary amides gave improved results (entries 6 and 7), with dibenzylamide-containing ligand **L5** giving the product in >95% conversion, 92% isolated yield, and 95% ee (entry 7). In contrast, ligand **L6** containing only one benzyl group on the amide nitrogen atom afforded inferior results (entry 8), further suggesting that under these conditions, a tertiary amide in the ligand is beneficial for high conversion. Finally, (*R*)-BINAP (**L7**) was tested for comparison and although the enantioselectivity was high, the reaction did not go to completion (entry 9). On the basis of these results, ligand **L5** was selected for further study.

Next, the addition of a range of arylboronic acids to various alkenyl-*p*-nitroarenes was investigated (Table 2), and the enantioselectivity of the reaction was, in most cases, high (84–97% ee). In addition to a *p*-nitrophenyl group (entries 1–12), other arenes that provide effective activation in this process include *o*-fluoro-*p*-nitrophenyl (entry 14), *m*-methyl-*p*-nitrophenyl (entry 15), *m*-carbomethoxy-*p*-nitrophenyl (entry 16),

Table 1 Ligand optimization for the asymmetric arylation of **1a**^a



Entry	Ligand	Conversion (%) ^b	ee (%) ^c
1	— ^d	42	n/a
2	L1	35	97
3 ^e	L1	70	95
4	L2	24	95
5	L3	76	70
6	L4	84	87
7	L5	>95 ^f	95
8	L6	44	90
9	L7	66	97

^a Reactions were conducted using 0.20 mmol of **1a** in dioxane (0.5 mL) and H_2O (0.1 mL). ^b Determined by ^1H NMR analysis of the unpurified reaction mixtures. ^c Determined by HPLC analysis on a chiral stationary phase. ^d $[\text{Rh}(\text{cod})\text{Cl}]_2$ was used in place of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, without an additional chiral ligand. ^e Reaction conducted at 120 °C for 30 min. ^f Product **2a** was isolated in 92% yield.

Table 2 Catalytic asymmetric arylation of alkenyl-*p*-nitroarenes^a

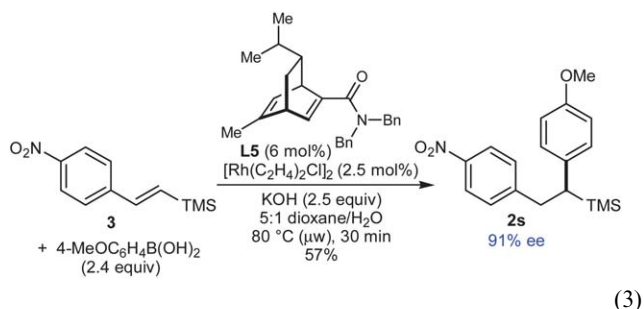
			Substrates: 					
Entry	Product	Yield (%) ee (%)	Entry	Product	Yield (%) ee (%)	Entry	Product	Yield (%) ee (%)
1		92 (90) ^b 95 (94) ^b	7		89 94	13		0 —
2		79 89	8		81 94	14		90 88
3 ^c		83 95	9		83 93	15 ^c		79 87
4		87 94	10		74 92	16		80 91
5		90 92	11		82 91	17		85 92
6 ^d		61 97	12		85 91	18		54 84

^a Unless otherwise stated, reactions were conducted using 0.20 mmol of **1a–1k**. Cited yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. ^b Values in parentheses refer to a reaction conducted under thermal heating under otherwise identical conditions. ^c Reaction performed using 1.0 mmol of **1b** at 80 °C under thermal heating for 1 h, using 2.5 mol% of Rh and 3 mol% of **L5**. ^d Reaction time was 1 h. ^e Reaction performed using 1.0 mmol of **1h**.

and *p*-nitro-*m*-(trifluoromethyl)phenyl (entry 17). The reaction is not limited to alkenyl-*p*-nitrobenzenes; substrate **1k** containing a 4-nitronaphthyl group also underwent arylation to provide **2r**, though the yield and enantioselectivity were somewhat diminished with this sterically more demanding substrate (entry 18). The range of tolerated substituents at the β-position of the alkene include simple linear alkyl groups (entries 1–9 and 14–18), a cyclopropyl group (entry 10), an allyl ether (entry 11) and an allyl amine (entry 12). However, a β-aryl group was found to inhibit the reaction (entry 13). Regarding the scope of the nucleophile, arylboronic acids containing methyl, halogen,

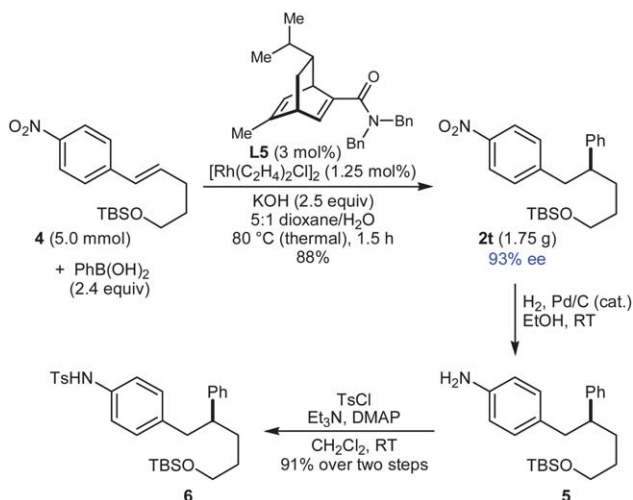
or methoxy substituents were competent reaction partners in this process. The reaction of sterically demanding 2-methylphenylboronic acid with substrate **1b** provided **2f** in 97% ee, though in a modest 61% yield (entry 6). Thermal heating is as effective as microwave heating, as evidenced by a reaction conducted under otherwise identical conditions (entry 1, values in parentheses). Furthermore, thermal heating was employed in the addition of phenylboronic acid to **1b** on a 1.0 mmol scale with 1.25 mol% of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ and 3 mol% of **L5** at 80 °C for 1 h, which provided **2c** in 83% yield and 95% ee (entry 3).

An additional demonstration of the reaction scope is provided in eqn (3), where substrate **3** containing a β -trimethylsilyl substituent underwent arylation in 57% yield and 91% ee.³¹



To further test the utility of this process, a preparative-scale reaction was performed using substrate **4** (5.0 mmol) containing an oxygenated alkyl substituent at the β -position (Scheme 1). This experiment provided **2t** in 88% yield and 93% ee. In addition, reduction of the nitro group of **2t**, followed by tosylation of the resulting amine **5**, provided sulfonamide **6** in 91% yield over two steps, the absolute stereochemistry of which was determined by single crystal X-ray analysis (Fig. 1).³² The sense of enantioinduction observed using ligand **L5** is consistent with the stereochemical model proposed for previously reported examples of arylation of acyclic electron-deficient alkenes using structurally similar chiral dienes.^{4,30} In this model, the rhodium–aryl bond is situated *trans* to the more electron-deficient alkene, and binding of the alkenylnitroarene occurs in a manner that minimizes unfavorable steric interactions (Fig. 2).

Nitroarenes are well-known to undergo a range of valuable reactions, making them versatile intermediates in the preparation of dyes, pharmaceuticals, and other functional compounds.³³ To demonstrate the synthetic utility of the arylation products described herein, **2o** was smoothly converted into indole **7** in 67% yield by treatment with vinylmagnesium bromide according to the method of Bartoli and co-workers (eqn (4)).^{34,35}



Scheme 1 Larger-scale arylation of **4** and subsequent elaboration.

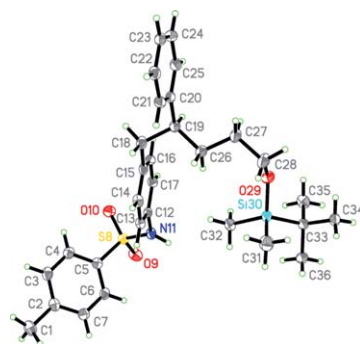


Fig. 1 An ORTEP drawing of **6** with ellipsoids set at 50% probability.

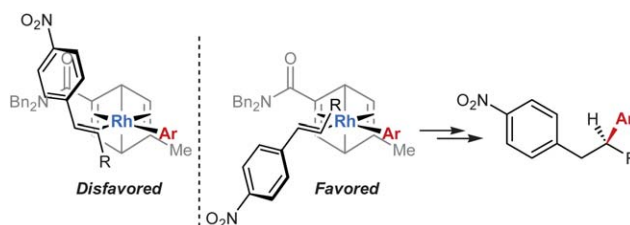


Fig. 2 A model for stereochemical induction.



Further experiments provided insights into the structural features required in the substrate for the reaction to proceed under the present conditions. Substrates **8** and **9** containing *m*-nitrophenyl and *o*-nitrophenyl groups, respectively, did not provide the desired arylation products (Fig. 3).

While the lack of reactivity of **8** is not surprising given that the nitro group is not conjugated with the alkene,^{6d} the failure of **9** to undergo arylation was somewhat unexpected, given that *o*-nitrostyrene has been shown to react smoothly with a variety of active methylene compounds under basic conditions.^{6d} The attempted arylation of **9** using a stoichiometric quantity of the rhodium–ligand complex also provided no evidence of the desired product, suggesting that the problem is one of reactivity rather than catalyst turnover. The addition of 10 mol% of substrate **9** to a repeat of the reaction of Table 2, entry 1 under otherwise identical conditions led to the formation of **2a** in >95% conversion and 94% ee, further suggesting that **9** does not poison the catalyst. Exactly how the *o*-nitro group in **9** inhibits the carboration step in the mechanism of rhodium-catalyzed addition of arylboronic acids to electron-deficient alkenes³⁶ is not known at this time.

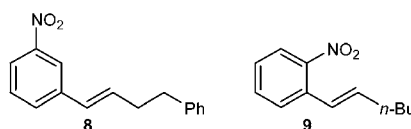
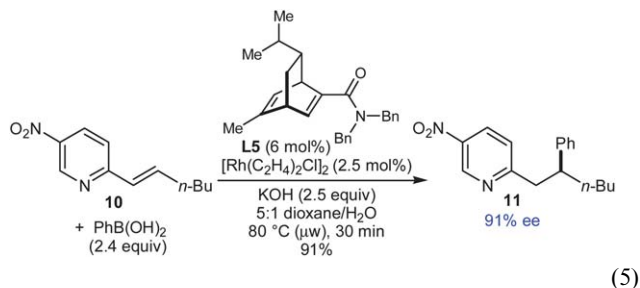
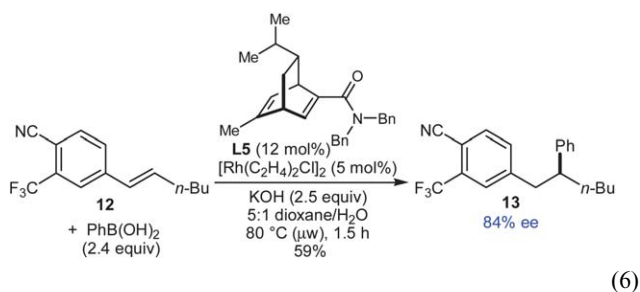


Fig. 3 Unreactive substrates.

Nevertheless, the powerful effect of a *p*-nitro group allowed us to address a problem discovered during our recent study of enantioselective rhodium-catalyzed additions of arylboronic acids to alkenylheteroarenes, which identified a 2-pyridyl group as providing insufficient activation of an adjacent alkene for arylation to proceed efficiently.⁴ Gratifyingly, 2-alkenylpyridine **10** containing a 5-nitro group underwent arylation in high yield and enantioselectivity (eqn (5)).



Finally, efforts to employ alkenylbenzene substrates containing a single *para*-electron-withdrawing substituent other than a nitro group, such as acetyl, nitrile, or methanesulfonyl, were unsuccessful with only low conversions into mixtures of identified products being observed. However, substrate **12**, containing a *p*-cyano-*m*-(trifluoromethyl)phenyl group, did undergo arylation in 59% yield and 84% ee in the presence of 10 mol% of the rhodium-chiral diene complex after 1.5 h (eqn (6)).



In contrast, no reaction was observed using (*R*)-BINAP (**L7**) as the ligand. The result of eqn (6) suggests that there is scope to increase the range of electron-deficient arenes that can be used as activating groups and future developments in this area may rest upon the identification of more active catalysts and/or improved reaction conditions.

Conclusions

In summary, highly enantioselective rhodium-catalyzed additions of arylboronic acids to alkenyl-*p*-nitroarenes and an alkenyl-*p*-cyano-*m*-(trifluoromethyl)arene have been developed. These reactions represent, to the best of our knowledge, the first examples of catalytic asymmetric additions of air- and moisture-stable organometallic reagents to alkenes activated by electron-deficient arenes. Extension of this concept to other classes of reactions may present exciting new opportunities for asymmetric catalysis. Studies in this area are under way and will be reported in due course.

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Enantioselective Copper-Catalyzed Reductive Coupling of Alkenylazaarenes with Ketones

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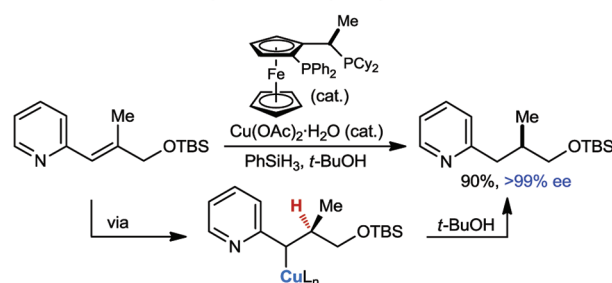
Supporting Information

ABSTRACT: Catalytic enantioselective methods for the preparation of chiral azaarene-containing compounds are of high value. By combining the utility of copper hydride catalysis with the ability of C=N-containing azaarenes to activate adjacent alkenes toward nucleophilic additions, the enantioselective reductive coupling of alkenylazaarenes with ketones has been developed. The process is tolerant of a wide variety of azaarenes and ketones, and provides aromatic heterocycles bearing tertiary-alcohol-containing side chains with high levels of diastereo- and enantioselecton.

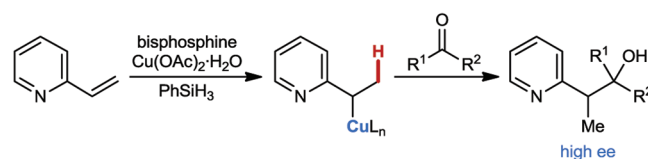
The development of new catalytic reactions for the functionalization of aromatic heterocycles and their derivatives continues to be a valuable endeavor due to the importance of these structures in natural products, pharmaceuticals, agrochemicals, and other molecules of interest. In this regard, recent efforts from our laboratory have targeted the development of processes that exploit the ability of a suitably positioned C=N moiety within azaarenes to activate adjacent alkenes toward catalytic enantioselective nucleophilic additions.^{1–3} The first of these reports described copper-catalyzed reductions⁴ of β,β -disubstituted 2-alkenylazaarenes, which result in alkylazaarenes with a new stereogenic center at the β -carbon (representative example in Figure 1A).¹ Since these reactions likely proceed via the intermediacy of organocopper species that undergo protonation with *t*-BuOH, we questioned whether these intermediates could be trapped in situ with an alternative electrophile such as a ketone (Figure 1B). Such a reductive coupling process would be synthetically more valuable, delivering more complex tertiary-alcohol-containing products with stereochemistry at both α - and β -carbons.

Although the proposed process is related to copper-catalyzed reductive aldol reactions described previously,^{5–9} to our knowledge, there are no reports of alkenylazaarenes being employed as substrates in these reactions. To date, the only report of catalytic reductive coupling reactions of alkenylazaarenes is that from the Krische group, who described racemic rhodium-catalyzed hydrogenative coupling of vinylazines with *N*-sulfonylaldimines (Figure 1C).¹⁰ The realization of *enantioselective* variants of this and related processes would therefore be of obvious value. Herein, we report highly enantioselective copper-catalyzed reductive coupling reactions of alkenylazaarenes with ketones.

A. Reduction of alkenylazaarenes (ref. 1)



B. Reductive coupling of alkenylazaarenes with ketones (this work)



C. Existing reductive coupling of vinylazines (ref. 10)

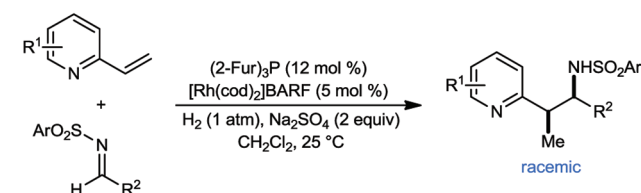
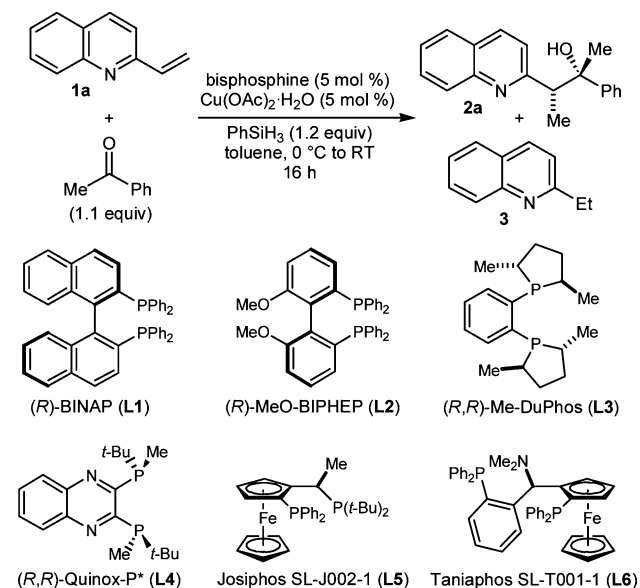


Figure 1. Catalytic transformations of alkenylazaarenes.

This study began with examination of the enantioselective reductive coupling of 2-vinylquinoline (**1a**) with acetophenone (1.1 equiv) using PhSiH₃ (1.2 equiv) as the hydride source, 5 mol % Cu(OAc)₂·H₂O, and 5 mol % of various chiral bisphosphines in toluene (Table 1).⁴ Pleasingly, proof of concept was quickly established, and all ligands evaluated led to complete consumption of **1a** to provide the coupling product **2a** as a mixture of diastereomers, along with traces of the simple reduction product **3**.¹¹ Enantioselectivities were modest using ligands **L1**–**L3** (entries 1–3), but high using (*R,R*)-Quinox-P* (**L4**) (entry 4), the Josiphos ligand **L5** (entry 5), and the Taniaphos ligand **L6** (entry 6). However, no diastereoselectivity was observed in most cases, with the notable exception being the reaction using **L6** which provided **2a** in 5:1 dr and

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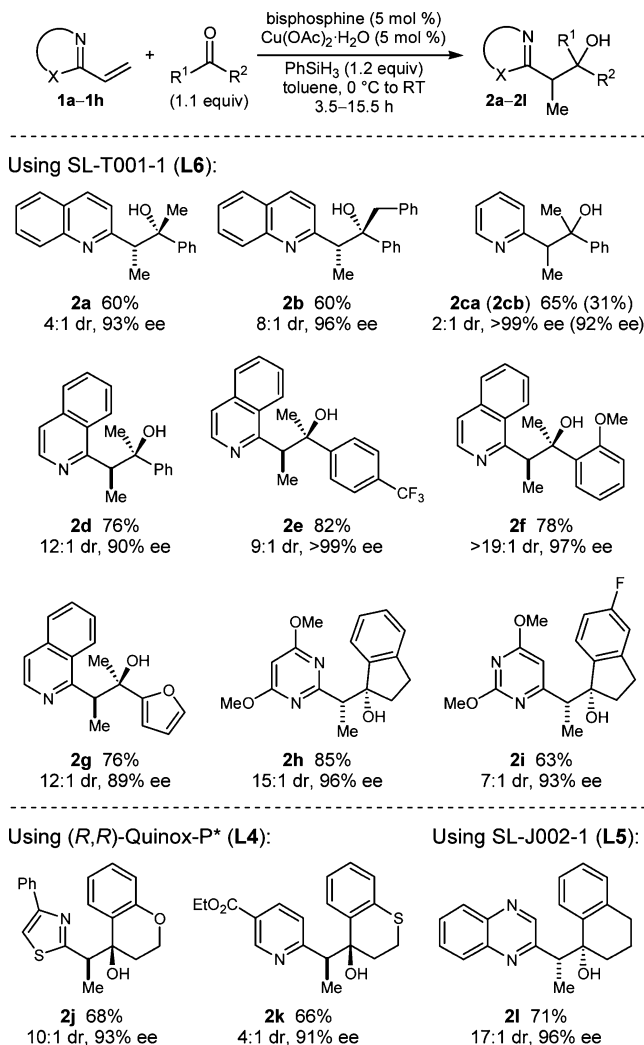
Table 1. Evaluation of Chiral Bisphosphines^a

entry	bisphosphine	2a:3 ^b	dr ^b	ee (%) ^c
1	L1	11:1	1:1	43, 50
2	L2	13:1	1:1	67, 67
3	L3	24:1	1:1	27, 17
4	L4	17:1	1:1	−60, −92
5	L5	12:1	1:1	92, 93
6	L6	7:1	5:1	93, 60

^aReactions were conducted using 0.10 mmol of **1a**. ^bDetermined by ¹H NMR analysis of the unpurified reaction mixtures. ^cDetermined by chiral HPLC analysis.

93% ee for the major isomer (entry 6). Accordingly, **L6** was selected for further experimentation.

Chart 1 presents results of reductive coupling of various vinylazaarenes **1a–1h**¹² with a range of ketones. Gratifyingly, the scope of the process is broad, and the enantioselectivities of the products were uniformly high (89–>99% ee).¹¹ Although **L6** provided the best results for products **2a–2i**, this ligand resulted in a low yield in the attempted synthesis of **2j**, and poor diastereo- and enantioselectivities in the attempted syntheses of **2k** and **2l**. In these cases, (*R,R*)-Quinox-P* (**L4**) was superior for **2j** and **2k**, and the Josiphos ligand **L5** was optimal for **2l**. In addition to **1a**, effective substrates include those containing azines such as pyridines (products **2c** and **2k**), isoquinoline (products **2d–2g**), two different isomeric dimethoxypyrimidines (products **2h** and **2i**), and quinoxaline (product **2l**). A vinylthiazole also smoothly underwent the reaction (product **2j**). With acyclic ketones, the diastereoselectivity of the reaction appears to be dependent on the steric properties of the azaarene, with diastereoselectivity increasing from pyridine to quinoline to isoquinoline (compare diastereomeric ratios for products **2c**, **2a**, and **2d**). In the coupling of 2-vinylpyridine with acetophenone, the two diastereomeric products **2ca** and **2cb** were isolated with high enantioselectivities (>99% and 92% ee, respectively). Regarding the electrophile, the process is tolerant of acyclic ketones containing various alkyl, aryl, or heteroaryl substituents (products **2a–2g**). In addition, cyclic ketones are viable substrates, as exemplified by the successful use of two indanones (products **2h** and **2i**), 4-chromanone (product **2j**), 4-thiochromanone (product **2k**), and tetralone (product **2l**).

Chart 1. Reaction Scope with Vinylazaarenes^a

^aReactions were conducted using 0.30–0.40 mmol of **1a–1h**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

Interestingly, the absolute stereochemistries of isoquinoline-containing products **2d–2g** are opposite to those of quinoline-containing products **2a** and **2b**, even though the same enantiomer of ligand **L6** was employed throughout.¹¹ In addition, the diastereochemical outcomes of the reactions producing **2h–2l** are different from those resulting in **2a**, **2b**, and **2d–2g**.¹¹ Assuming that the reactions proceed via Zimmerman–Traxler-type transition states where the larger aryl group of the ketone occupies a pseudoequatorial position,¹³ Figure 2 depicts conformations that are consistent with these observations. The stereochemical outcomes of the reactions producing **2a**, **2b**, and **2d–2g** are consistent with the participation of *Z*-azaallylcopper species¹⁴ (**TS 1** and **TS 2**), though the reasons for the opposite sense of enantioinduction in **TS 2** compared with **TS 1** are not clear at this time. Furthermore, while the preference for the *Z*-azaallylcopper species in **TS 2** is readily explained by the severe A_{1,3}-strain¹⁵ that would disfavor the corresponding *E*-azaallylcopper species, a similar argument cannot be used to explain the same preference in **TS 1**. For reactions producing **2h–2l**, reaction

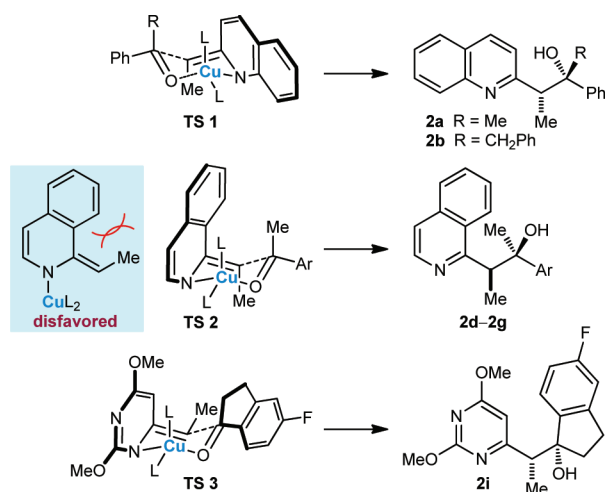
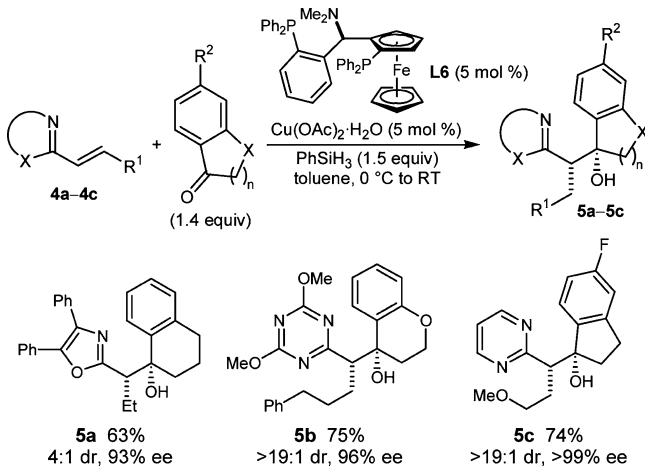


Figure 2. Rationalization of stereochemical outcomes.

through the *E*-azaallylcopper species (or *Z*-azaallylcopper species in the case of **2j**) appears to be favored, as in TS 3 for the formation of **2i**. The interplay between the steric and/or electronic properties of the alkenylazaarene and the ligand and the resulting effect on the stereochemical outcome are clearly complex. In addition, while the preceding discussion has been based upon the assumption that chairlike transition states are operative, reaction through boatlike structures cannot be excluded.

Notably, the process is not limited to vinylazaarenes; β -substituted alkenylazaarenes are also effective coupling partners (Chart 2). For example, alkenylazaarenes **4a–4c**¹² containing

Chart 2. Reductive Coupling of β -Substituted Alkenylazaarenes with Ketones^a



^aReactions were conducted using 0.30 mmol of **4a–4c**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

methyl, phenethyl, or allylic ether groups smoothly underwent reductive coupling to deliver products **5a–5c**, respectively, in high enantioselectivities.¹¹ Furthermore, these products contain additional examples of azaarenes not utilized in Chart 1, such as diphenyloxazole (product **5a**), a dimethoxytriazine (product **5b**), and 1,3-pyrimidine (product **5c**).

In summary, we have described the first examples of catalytic enantioselective reductive couplings of alkenylazaarenes. The scope of this process is broad, with 11 different types of azaarenes and a range of acyclic and cyclic ketones having been shown to be effective coupling partners. β -Substitution on the alkene is tolerated, and the reactions proceed under mild conditions to deliver products in good to high levels of diastereo- and enantioselection. These features should be advantageous for application of this process in the preparation of novel enantioenriched chiral azaarene-containing building blocks.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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